Trial Design and Reporting Standards for Intra-Arterial Cerebral Thrombolysis for Acute Ischemic Stroke

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Background and Purpose—The National Institutes of Health (NIH) estimates that stroke costs now exceed $45 billion per year. Stroke is the third leading cause of death and one of the leading causes of adult disability in North America, Europe, and Asia. A number of well-designed randomized stroke trials and case series have now been reported in the literature to evaluate the safety and efficacy of thrombolytic therapy for the treatment of acute ischemic stroke. These stroke trials have included intravenous studies, intra-arterial studies, and combinations of both, as well as use of mechanical devices for removal of thromboemboli and of neuroprotectant drugs, alone or in combination with thrombolytic therapy. At this time, the only therapy demonstrated to improve outcomes from an acute stroke is thrombolysis of the clot responsible for the ischemic event. Therefore targeted to help an investigator to critically review the scales and scores used previously in stroke trials.

Methods—This article was written under the auspices of the Technology Assessment Committees for both the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology. The purpose of this document is to provide guidance for the ongoing study design of trials of intra-arterial cerebral thrombolysis in acute ischemic stroke. It serves as a background for the intra-arterial thrombolytic trials in North America and Europe, discusses limitations of thrombolytic therapy, defines predictors for success, and offers the rationale for the different considerations that might be important during the design of a clinical trial for intra-arterial thrombolysis in acute stroke.

Included in this guidance document are suggestions for uniform reporting standards for such trials. These definitions and standards are mainly intended for research trials; however, they should also be helpful in clinical practice and applicable to all publications.

This article serves to standardize reporting terminology and includes pretreatment assessment, neurologic evaluation with the NIH Stroke Scale score, imaging evaluation, occlusion sites, perfusion grades, follow-up imaging studies, and neurologic assessments. Moreover, previously used and established definitions for patient selection, outcome assessment, and data analysis are provided, with some possible variations on specific end points. This document is therefore targeted to help an investigator to critically review the scales and scores used previously in stroke trials.
This article also seeks to standardize patient selection for treatment based on neurologic condition at presentation, baseline imaging studies, and utilization of standardized inclusion/exclusion criteria. It defines outcomes from therapy in phase I, II, and III studies. Statistical approaches are presented for analyzing outcomes from prospective, randomized trials with both primary and secondary variable analysis. A discussion on techniques for angiography, intra-arterial thrombolysis, anticoagulation, adjuvant therapy, and patient management after therapy is given, as well as recommendations for posttreatment evaluation, duration of follow-up, and reporting of disability outcomes.

Imaging assessment before and after treatment is given. In the past, noncontrast CT brain scans were used as the initial screening examination of choice to exclude cerebral hemorrhage. However, it is now possible to quantify the volume of early infarct by using contiguous, discrete (nonhelical) images of 5 mm. In addition, CT angiography by helical scanning and 100 mL of intravenous contrast agent can be used expeditiously to obtain excellent vascular anatomy, define the occlusion site, obtain 2D and 3D reformatted vascular images, grade collateral blood flow, and perform tissue-perfusion studies to define transit times of a contrast bolus through specific tissue beds and regions of interest in the brain. Dynamic CT perfusion scans to assess the whole dynamics of a contrast agent transit curve can now be routinely obtained at many hospitals involved in these studies. The rationale, current status of this technology, and potential use in future clinical trials are given.

Many hospitals are also performing MR brain studies at baseline in addition to, or instead of, CT scans. MRI has a high sensitivity and specificity for the diagnosis of ischemic stroke in the first several hours from symptom onset, identifies arterial occlusions, and characterizes ischemic pathology noninvasively. Case series have demonstrated and characterized the early detection of intraparenchymal hemorrhage and subarachnoid hemorrhage by MRI. Echo planar images, used for diffusion MRI and, in particular, perfusion MRI are inherently sensitive for the susceptibility changes caused by intraparenchymal blood products. Consequently, MRI has replaced CT to rule out acute hemorrhage in some centers. The rationale and the potential uses of MR scanning are provided.

In addition to established criteria, technology is continuously evolving, and imaging techniques have been introduced that offer new insights into the pathophysiology of acute ischemic stroke. For example, a better patient stratification might be possible if CT and/or MRI brain scans are used not only as exclusion criteria but also to provide individual inclusion and exclusion criteria based on tissue physiology. Imaging techniques might also be used as a surrogate outcome measure in future thrombolytic trials. The context of a controlled study is the best environment to validate emerging imaging and treatment techniques.

The final section details reporting standards for complications and adverse outcomes; defines serious adverse events, adverse events, and unanticipated adverse events; and describes severity of complications and their relation to treatment groups. Recommendations are made regarding comparing treatment groups, randomization and blinding, intention-to-treat analysis, quality-of-life analysis, and efficacy analysis.

This document concludes with an analysis of general costs associated with therapy, a discussion regarding entry criteria, outcome measures, and the variability of assessment of the different stroke scales currently used in the literature is also featured.

**Conclusion**—In summary, this article serves to provide a more uniform set of criteria for clinical trials and reporting outcomes used in designing stroke trials involving intra-arterial thrombolytic agents, either alone or in combination with other therapies. It is anticipated that by having a more uniform set of reporting standards, more meaningful analysis of the data and the literature will be able to be achieved. *(Stroke. 2003;34:e109-e137.)*

**Key Words:** stroke, ischemic ▪ thrombolysis ▪ trial design

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stroke is the third leading cause of death in the United States, Canada, Europe, and Japan. According to the American Heart Association and the American Stroke Association, there are now >700 000 new strokes that occur each year, resulting in >200 000 deaths per year in the United States alone. Ischemic stroke accounts for 80% and hemorrhagic stroke accounts for 20% of this total. Stroke is the leading cause of adult disability in North America and the No. 1 cause for inpatient Medicare reimbursement for long-term adult care. The National Institutes of Health (NIH) estimates that stroke costs now exceed $45 billion in US healthcare dollars per year. At this time, the only therapy demonstrated to improve outcomes from acute ischemic stroke is thrombolysis of the clot responsible for the ischemic event. Intravenous (IV) thrombolysis has been studied in multiple trials, as described subsequently. Intra-arterial (IA) thrombolysis has been studied in 2 randomized trials and multiple case series. The purpose of this document is to provide guidance on study design for trials of IA cerebral thrombolysis of acute ischemic stroke. Included in this guidance document are reporting standards for such trials. Although many of the definitions and standards might be helpful in clinical practice, the study design recommendations are mainly intended for research trials. Many of the study design recommendations might also not be applicable for publications involving case series rather than controlled trials. However, the reporting standards should be applicable to all publications.

**IV Trials in Acute Ischemic Stroke**

In the late 1980s and 1990s, 8 large, well-designed, multi-center trials of IV thrombolysis were reported. Three initial
trials of IV streptokinase (SK) in acute ischemic stroke, within 4 to 6 hours from symptom onset, were stopped by their safety committees owing to a high rate of acute mortality and intracranial hemorrhage (ICH) in the treatment arm. These included the Multicenter Acute Stroke Trial-Europe (MAST-E), the Australian Streptokinase Trial (ASK), and the Multicenter Acute Stroke Trial-Italy (MAST-I). Five other major studies evaluated the use of IV recombinant tissue plasminogen activator (rtPA) for acute stroke, from 3 to 6 hours from symptom onset, and included 2 trials sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), the European Cooperative Acute Stroke Study (ECASS-I and ECASS-II), and the Alteplase Thrombolysis for Acute Noninterventional Therapy (ATLANTIS).10

The only 2 successful IV thrombolysis stroke trials to date have been the NINDS rtPA trials. These were placebo-controlled, randomized trials, performed as 2 separate studies, with 0.9 mg/kg rtPA given IV within 3 hours of symptom onset. Enrollment was completed in the first trial before starting the second trial with nearly identical design, including the same outcome measures but different prespecified end points. For practical reasons, the 2 trials were designated as Part A and Part B and analyzed as a meta-analysis. Nonetheless, they had extremely similar results, each successful in indicating superior outcomes for IV rtPA. The NINDS trial was a nonangiographic study involving 624 patients and included all ischemic stroke subtypes (small-vessel, large-vessel, and cardioembolic) of any degree or severity (median NIH Stroke Scale [NIHSS] score 14). Blood pressure was carefully controlled and maintained at <185/110 mm Hg. Patients meeting all entry criteria were treated with IV rtPA within 3 hours and were at least 30% more likely to have minimal or no disability at 3 months than were patients who received placebo. Benefit was seen in all stroke subtypes. Post hoc analysis failed to reveal any subgroup that did not benefit from IV thrombolysis, although the magnitude of improvement was less in elderly patients with severe strokes. However, there was a 10-fold increased risk of symptomatic brain hemorrhage within the first 36 hours: 6.4% in the rtPA group versus 0.6% in the placebo group (P=0.001). Although half of the brain hemorrhages were fatal, there were no differences in overall mortality between the 2 treatment groups. Early brain computed tomography (CT) changes of infarction and more severe neurologic deficit (NIHSS>20) were associated with an increased risk of symptomatic brain hemorrhage. The favorable outcome of these 2 NINDS-sponsored trials constituted the basis for US Food and Drug Administration (FDA) approval of IV rtPA in June 1996 for patients presenting with an ischemic stroke within 3 hours of symptom onset. To date, these 2 NINDS rtPA stroke trials have been the only positive, multicenter, randomized, controlled acute stroke studies in which IV lytics have been used.

ECASS-I was a multicenter, controlled study of IV rtPA for acute ischemic stroke conducted at 75 centers in Europe. A slightly higher dose of rtPA, 1.1 mg/kg, and a longer time window, 6 hours, were used in ECASS-I. Other important differences between ECASS and the NINDS trial were the inclusion of patients with moderate to severe hemispheric strokes only and the exclusion of patients with early CT changes involving more than one third of the territory of the middle cerebral artery (MCA). Despite careful selection of patients by trial examiners, 17.4% of the patients enrolled (109 of 620) had serious protocol violations, and more than half had major early infarct signs on CT. There was no benefit in the “intention-to-treat” (ITT) population in primary outcome by use of measures of functional outcome (the Barthel Index [BI] and modified Rankin Scale score [mRSS]) at 3 months. There was a “trend for improvement” in patients treated with rtPA within 3 hours of stroke onset. All of the secondary end points were significantly improved in the rtPA group, including speed of neurologic recovery, in-hospital stay, and the combined mRSS-BI score. Parenchymal hematomas occurred in 19.8% of the rtPA group and in 6.5% of the placebo group (P<0.001). Mortality was also significantly worse at 90 days in the rtPA-treated patients (P=0.04). Outcome was especially poor in the protocol violators who received rtPA, in which 42% died. Although the ITT analysis was negative, ECASS defined a “target” population by excluding protocol violators. In the target population, there was a significant improvement in the 90-day RSS (a primary outcome measure) in rtPA-treated patients (P=0.035). Also, when the NINDS statistical methodology was applied to the ECASS ITT dataset, there was a significant increase in favorable outcome in rtPA-treated patients, similar in degree to that seen in the NINDS study.

The ECASS II trial was a second attempt to demonstrate the efficacy of the 6-hour time window of IV rtPA for acute ischemic stroke. ECASS-II reduced the IV rtPA dose to 0.9 mg/kg (as in the NINDS trial). All participating sites underwent CT training sessions, and the rate of CT violations was reduced by 50%. Blood pressure parameters were also more tightly controlled. The parenchymal hemorrhage rate in patients receiving IV rtPA (11.8%) was lower than that seen in ECASS-I, although it was still 4 times more common than in placebo-treated patients (3.1%). Protocol violations declined to 9%. Unfortunately, there was no significant difference in the percentage of patients achieving the primary outcome measure of minimal or no disability (mRSS of 0 to 1 at 90 days) between the IV rtPA patients (40.3%) and the control group (36.6%, P=0.277). This reflected the better-than-expected outcome in the placebo arm. A post hoc analysis did demonstrate a significant (8%) increase in patients with slight or no disability (mRSS of ≥2) among treated patients.

The ATLANTIS trial10,11 was also designed to demonstrate that the time window for IV rtPA administration could be extended to 3 to 6 hours from symptom onset. However, because of a high rate of brain hemorrhages, the treatment window was eventually decreased to 3 to 5 hours from stroke onset. The inclusion and exclusion criteria for this multicenter, randomized trial were very similar to those of the NINDS trial, except for the time window and exclusion of patients with early infarct signs of more than one third of the MCA territory, which was learned from the ECASS-I study. This trial was halted prematurely, after 63% of the planned patients had been enrolled, when an interim analysis indicated that treatment was unlikely to prove beneficial. Symptomatic
intracerebral hemorrhage (ICH) occurred in 7% of IV rtPA patients versus 1.1% in the placebo group (P<0.001). However, in the 61 patients who were randomized to IV rtPA or placebo within 3 hours of symptom onset, there was a statistically significant 35% absolute increase in the number of patients with an NIHSS score of ≤1. Symptomatic (and fatal) ICHs occurred in 13% of treated patients and 0% of placebo patients. The death rate was more than 3 times higher in treated patients (17% versus 5%), but with the small numbers of patients involved, this difference did not reach statistical significance.12

**IA Trials in Acute Ischemic Stroke**

IA thrombolysis provides an alternative to IV thrombolysis in selected patients with acute ischemic stroke. Recent advances in the field of neurointerventional radiology, with the development of extremely soft, compliant microcatheters and steerable microguidewires; high-resolution fluoroscopy and digital imaging; and nonionic contrast agents, have made it feasible and safe to access the major intracranial blood vessels around the circle of Willis from a percutaneous transfemoral approach under local anesthesia. Rapid, local delivery of fibrinolytic agents or immediate access of thrombolytic devices is now feasible with these techniques and is performed at many major medical centers in selected patients with acute cerebral ischemia.

IA thrombolysis has been used most successfully in patients with acute MCA occlusion. There is evidence that the treatment window for IA thrombolysis with these techniques can be extended to at least 6 hours from stroke onset in patients with MCA occlusion. Other potential candidates for IA thrombolysis include patients with extracranial internal carotid artery (ICA) occlusion, intracranial carotid artery “T” occlusion, or basilar artery occlusion. Initial clinical and radiologic patient selection criteria and definition of outcome, as well as pretreatment and posttreatment evaluation, are mostly identical for IV and IA trials, although treatment description and complications differ significantly. Two randomized, multicenter, controlled trials of IA thrombolysis in acute MCA stroke have been reported so far, the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT-I)13 and PROACT-II.14

Recanalization efficacy and safety of IA recombinant pro-urokinase (r-proUK) for MCA occlusion of <6 hours’ duration was demonstrated in the PROACT-I trial.15 The follow-up clinical efficacy trial, PROACT-II,14 was started in February 1996 and completed in August 1998. PROACT-II used an open design with blinded follow-up. Patients were screened with conventional angiography for occlusion of the MCA and had to have an NIHSS score between 4 and 30. The patients in PROACT-II had a very high baseline stroke severity with a median NIHSS of 17. Patients with early signs of an infarct in more than one third of the MCA territory on the baseline CT scan were excluded from the study. In PROACT-II, 180 patients were randomized 2:1 to receive either 9 mg r-proUK directly into an angiographically documented MCA occlusion plus low-dose IV heparin (2000-U bolus + 500 U/h × 4 hours) or low-dose IV heparin only. The primary outcome measure was the percentage of patients who achieved an mRSS ≤2 at 90 days, which signified slight or no neurologic disability. Secondary measures included the percentage of patients who had an NIHSS ≤1 at 90 days, angiographic recanalization, symptomatic ICH, and mortality. The median time from onset of symptoms to initiation of IA thrombolysis was 5.3 hours. In the r-proUK–treated group, there was a 15% absolute benefit in the number of patients who achieved an mRSS ≤2 at 90 days (P=0.043). Therefore, on average, 7 patients with an MCA occlusion would require IA r-proUK for 1 to benefit for the primary end point of achieving an mRSS ≤2 (mild or no disability). However, it is quite possible that others might also benefit in ways not captured by the primary end point (eg, improvement from mRSS 2 to 1 or from 4 to 3). The benefit was most noticeable in patients with a baseline NIHSS between 11 and 20. Recanalization rates were 66% after the 2-hour infusion for the treatment group versus 18% for the placebo group (P<0.001). Symptomatic brain hemorrhage occurred in 10% of the r-proUK group versus 2% in the control group. In PROACT-II, as in the NINDS trial, despite the higher early symptomatic brain hemorrhage rate, patients overall benefited from therapy, and there was no excess mortality (r-proUK 24%, control 27%) in the ITT analysis. The results of PROACT-II, though encouraging, were insufficient to secure FDA approval of r-proUK. The FDA has requested another larger trial of IA thrombolysis. Based on the available evidence, IA thrombolysis has been endorsed by several national organizations as an acceptable alternative stroke therapy in selected patients with acute ischemic stroke.

A third randomized trial was the Emergency Management of Stroke (EMS) Bridging Trial. This phase 1 pilot trial randomized patients either to treatment with reduced-dose IV alteplase, followed by arteriography, with IA infusion of up to 22 mg of alteplase if an appropriate arterial occlusive lesion was discovered (IV/IA), or placebo followed by IA lysis. In one third of cases, arteriography did not confirm the clot. Overall, of 15 patients with M1 or M2 occlusions, 66% good outcomes were achieved with a mean time to IA treatment of 4.2 hours. The IV/IA group had better recanalization than the IA group, but there was no difference in outcomes between the 2 treatment groups.15

**Limitations of IA Thrombolysis**

A major issue regarding access to IA thrombolysis to treat acute ischemic stroke is that it requires the ready availability of an endovascular interventionalist trained in IA thrombolysis and a stroke team. Such expertise is not currently available in most community hospitals across the United States and has usually been limited to large academic centers.16,17 Another limitation of IA thrombolysis is the additional time required to begin treatment compared with IV thrombolysis. In PROACT-II, the average time from arrival at the hospital to the initiation of IA r-proUK was 3 hours. The time from completion of the CT scan to the start of lytic therapy was in the range of 30 to 90 minutes. However, even for IV tPA, the CT to needle time reportedly ranges from 52 to 68 minutes.18,19 There are also concerns regarding the invasiveness of the technique and procedural risks not inherent to IV thrombolysis. However, serious procedural compli-
cations were uncommon in PROACT-I and II. Cerebral angiography in experienced centers is associated with a morbidity rate of 1.4% and a rate of permanent neurologic complications and death of 0.06% to 0.5%, respectively.20–23

Predictors for Treatment Success
One of the most important predictors of clinical success is time to treatment, with early treatment of <3 hours’ demonstrating significant improvement in terms of 90-day clinical outcome and reduced cerebral hemorrhage.8–11,13,14,16,17 However, there are remaining problems in the assessment of patients who are eligible for thrombolysis. These include being able to predict whether a particular occlusion can be successfully revascularized, an individual patient’s prognosis and outcome after revascularization, and in particular, the development of ICH, with and without clinical deterioration. These predictors are important in selecting the appropriate target population for lytic therapy.

The immediate parameter for assessing treatment success is to evaluate the achieved flow restoration. However, it is not clear to presume that technical success, ie, recanalization, necessarily implies clinical success, ie, improved outcome. There is no simple correlation between recanalization and observed clinical benefit in ischemic stroke. From a pathophysiologic viewpoint, arterial occlusion is the cause of the stroke, and the primary mechanism of action of thrombolysis is clot lysis, resulting in recanalization and reestablishment of distal blood flow. However, although many case series have reported a “general relationship” between recanalization and good clinical outcome, this relation is known to be complex and dependent on several interactive variables. Ringelstein et al24 reported that early recanalization of MCA occlusion within 8 hours of stroke onset had a favorable effect on infarct size and clinical outcome, but only in conjunction with good transcortical collateral blood flow. Von Kummer et al25 reported that MCA partial or complete recanalization at <8 hours had no independent predictive value for good outcome and did not independently affect mortality. However, recanalization, even if delayed to 24 hours, was associated with improved clinical outcome in a subset of the patients studied, who were characterized by less hypodensity on baseline CT, baseline lower neurologic assessment, proximal site of occlusion, and good collateral flow. Similarly, a post hoc analysis of the PROACT-II data found that the relation between recanalization and clinical outcome was dependent on the precise site of arterial occlusion and on collateral arterial supply.26 Improved outcome was associated with more distal occlusions and with better collateral flow demonstrated angiographically.

The appropriateness of using recanalization as a surrogate marker of outcome has had a correlation with recent diffusion and perfusion magnetic resonance (MR) studies. However, there is no direct correlation between recanalization and clinical outcome. Other factors in addition to recanalization, including baseline stroke severity, collateral circulation, lesion location, lesion volume, and time from stroke onset, are probably important in determining clinical outcome. Baird27 identified a perfusion-diffusion mismatch on MR imaging (MRI) within 24 hours of stroke onset in 90% of patients with an arterial-occlusive lesion (ICA or MCA) on MR angiography (MRA). A mismatch between the infarct lesion size as shown by diffusion-weighted imaging (DWI) and that shown by perfusion imaging might mark potentially salvageable ischemic brain tissue.28 Resolution of the mismatch, ie, a decrease in the size of the ischemic lesion, occurred in 75% of patients with arterial recanalization on follow-up MRA, compared with 36% of patients with persistent occlusion. MR perfusion-diffusion mismatch has been correlated with infarct growth and adverse clinical outcome.28,29

The recanalization rates and clinical outcomes of thrombolysis vary with the site of arterial occlusion and techniques involved in treatment. In general, thrombus confined to the MCA beyond the striate arteries or its distal branches has a much better outcome than when the thrombus also involves the supracilindar carotid artery segment and then extends into the proximal middle and anterior cerebral artery (T-lesion occlusions).30 Patients with ischemic stroke of <6 hours’ duration have a wide variety of arterial-occlusion sites, and 20% have no visible occlusion, despite similar neurologic presentations.14,30 In PROACT-II, 474 patients had a screening angiogram to enroll 180 eligible patients with proximal MCA occlusions.14 In the IV thrombolysis stroke trials, neither the sites of arterial occlusion nor the recanalization rates were known. Angiography performed during IA lysis permits documentation of both the site of arterial occlusion and recanalization rates and provides access for IA thrombolysis.

Recanalization rates with IA thrombolysis are superior to those for IV thrombolysis for major cerebrovascular occlusions. Recanalization rates for major cerebrovascular occlusions average 70% for IA thrombolysis compared with 34% for IV thrombolysis.31 The differences in recanalization rates are most apparent with large-vessel occlusions such as the ICA, which is the most difficult vessel for thrombolysis, followed by the carotid T segment and the proximal (M1) segment of the MCA.25

There have been no randomized studies comparing recanalization rates and clinical outcomes between IV thrombolysis and IA thrombolysis. Limited data suggest, however, that IV rtPA might be relatively ineffective in patients with ICA or MCA occlusion. Data from the TTATTS (Thrombolytic Therapy of Acute Thrombotic/Thromboembolic Stroke) study indicate that the recanalization rate for large-vessel occlusion with 0.8 mg/kg or 1.0 mg/kg IV rtPA is no more than 30% effective (personal communication). Tomski et al32 reported that IV rtPA given <3 hours from stroke onset was ineffective in patients with a baseline NIHSS score ≥10 and a hyperdense MCA sign (signifying MCA occlusion) on brain CT scans.

Prediction of hemorrhagic complications is another unresolved problem with thrombolytic treatment. Aggregate data indicate an 8.3% risk of symptomatic brain hemorrhage with IA thrombolysis in the carotid territory and a 6.5% risk in the verteobrobasilar territory.33 There is no evidence that the rate of symptomatic brain hemorrhage is lower with IA thrombolysis than with IV thrombolysis, but direct comparisons are difficult. In an uncontrolled series, Göninger et al34 reported a 4.7% rate of symptomatic brain hemorrhage in 42
patients treated with IA thrombolysis. This series differed from PROACT-II in that only 26 of the 42 patients received heparin; the remainder received aspirin. The higher rate of ICH causing neurologic deterioration with IA r-proUK in PROACT-II (10.2%) compared with IV rtPA in NINDS (6.4%)7 ATLANDIS (7.2%),10 and ECASS-II (8.8%)9 must be understood within the context of the greater baseline stroke severity, longer time to treatment, and 66% MCA recanalization rate in PROACT-II. However, although brain hemorrhage complicating thrombolysis for acute stroke likely reflects reperfusion of necrotic tissue, several series have found no direct relation between recanalization and hemorrhage risk.5,36 The amount of ischemic damage is a key factor in the development of brain hemorrhage after thrombolysis-induced recanalization. Major, early CT changes and severity of the initial neurologic deficit, both indicators of the extent of ischemic damage, are some of the best predictors of the risk of hemorrhagic transformation.5,36 The median baseline NIHSS score in ATLANTIS and ECASS-II was 11; in NINDS, 14; and in PROACT-II, 17. Greater baseline stroke severity was first associated with increased ICH risk in NINDS and ECASS-I. All symptomatic ICHs in PROACT-II occurred in patients with a baseline NIHSS score ≥11, and in NINDS, the rate of symptomatic brain hemorrhage in patients with an NIHSS >20 was 18%.

The dose of the thrombolytic agent,37 blood pressure,7,38,39 advanced age,39 prior head trauma,40 and blood glucose >200 mg/dL41 have been associated with hemorrhage after thrombolysis for both stroke and myocardial infarction. Adjunctive antithrombotic therapy might also play a role during IA thrombolysis. Age was the most important risk factor in 1 of the largest series of thrombolysis-related ICHs in patients treated for coronary occlusions.40 A relation between advanced age and hemorrhage was demonstrated in the NINDS36 and ECASS trials.8,9 Although there is no strict age cutoff for administering thrombolytics for stroke, physicians need to take age into account, especially in patients older than 75 years when determining the risk of angiography and IA thrombolysis.

Summary
Most lessons learned in previous studies have been immediately implemented in the protocol of a subsequent trial, eg, standardized baseline neurologic examination (the NIHSS score), exclusion of patients with extensive early CT signs, dose corrections for both thrombolytic agents and concomitant anticoagulation and antiplatelet medications, or training diagnostic radiologists and neurologists to accurately read screening CT brain scans. These should be standards for future thrombolytic trials and are mentioned in detail in the succeeding sections of this report.

Other exploratory analyses of thrombolytic studies create new hypotheses by recognizing parameters that might influence treatment success and outcome. For example, the precise clot location, even within the MCA territory, or the extent of tissue-preserving perfusion, eg, via collateral supply, is of importance. The interaction between the different clinical and radiologic parameters is complex, and their combined implication for treatment success and outcome is still the subject of ongoing investigations. To validate the importance of the different variables, they should be collected in upcoming trials and analyzed post hoc. These imaging-based criteria for the assessment of collateral flow might possibly override our current time-based selection rules for inclusion. For example, a patient with evidence of good collateral flow might still be a candidate for thrombolysis, even when presenting beyond the accepted time window of postsymptom onset, whereas patients without evidence of any collateral flow or tissue perfusion might be excluded from trials even when they present within the generally accepted time window. This document provides a framework of study design and reporting standards by which these new hypotheses might be evaluated.

Pretreatment Evaluation
To provide information necessary for defining patient selection, inclusion/exclusion criteria, and outcomes of therapy, it is necessary to describe the methods used to evaluate stroke patients before treatment. Such pretreatment evaluation includes general medical history and physical examination, neurologic history and examination, laboratory (blood) tests, and imaging.

General Medical Evaluation
A complete physical examination and medical history should be obtained at screening, including a detailed cardiovascular and cerebrovascular medical history. Blood pressure (3 successive measurements 10 minutes apart), pulse rate, and respiration rate should be obtained at screening. Any medication (including over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements and herbal preparations) that the subject has taken within 48 hours before enrollment or has received during the first 7 days (or hospital discharge) after enrollment should be recorded, along with the dates of administration, dose, and frequency.

A 12-lead ECG is recommended before the procedure, at 24 hours, and then at 48 to 72 hours after randomization when indicated. Samples for cardiac enzyme levels, to rule out acute myocardial ischemia/infarction, should be drawn as appropriate when any abnormal ECG changes are detected. In addition, cardiac echocardiography is recommended in all patients with a history of arrhythmias.

Laboratory Evaluation
Before angiography, blood specimens for the following laboratory studies should be obtained: (1) Hematology: hematocrit, hemoglobin, and platelet count; (2) Coagulation parameters: activated partial thromboplastin time (aPTT), prothrombin time, and international normalized ratio. In the event that the subject was receiving heparin therapy just before screening, an aPTT must be performed with a result ≤1.5 times the upper limit of normal before randomization;

Clinical chemistry: Tests of liver function (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase) when indicated; kidney function (creatinine, blood urea nitrogen), and serum glucose.
Neurologic Evaluation
Examples of neurologic impairment scales include the NIHSS,\(^{42}\) Canadian Neurologic Scale,\(^{43}\) and Scandinavian Stroke Scale.\(^{44}\) The NIHSS is a 42-point scale that quantifies neurologic function in specific categories and provides a means to measure neurologic deficits. Higher scores indicate a more severe neurologic deficit. The NIHSS was developed by researchers at the NINDS specifically for use in clinical stroke trials. The NIHSS has been extensively used in clinical trials to quantitatively measure stroke outcomes and has been validated and standardized to reduce interobserver error. Neurologic assessments should use the NIHSS. The screening NIHSS assessment should be used for subject entry restriction of NIHSS score. Screening NIHSS should be performed by an examiner experienced in acute stroke treatment who has achieved certification in administering the NIHSS. The NIHSS score should be determined again just before diagnostic cerebral angiography. If the NIHSS score has significantly improved from baseline, such as a ≥4-point improvement, or has improved below or increased above the defined threshold, the subject might not be eligible for randomization. The NIHSS was designed primarily for anterior-circulation ischemic stroke evaluation. It might underestimate the severity of deficit for posterior-circulation strokes, because posterior-circulation symptoms, such as vertigo or difficulty in swallowing, are not included on the NIHSS evaluation. A standardized grading system for posterior-circulation strokes is not currently available.

Disability and handicap scales include such instruments as the Barthel Index (BI) of Activities of Daily Living,\(^{35}\) the modified Rankin Scale (mRS),\(^{46}\) and the Stroke Impact Scale.\(^{47}\) There is a written examination to certify the examiner in administering the BI. There is no certification procedure for the mRS, which is the most commonly used global assessment of stroke outcome. All of these stroke outcome assessments are reliable, familiar to the stroke neurology community, and adaptable for use in patients with acute stroke and can be used to compare outcomes as end points when evaluating other published trials of thrombolytic therapy. The BI is used for functional evaluation to measure activities of daily living and has been used since 1955 as a simple index of independence by scoring the ability of patients with neuromuscular or musculoskeletal disorders and by evaluating progress in these patients. The BI scores patients in each of 10 listed activities, and a score of 10 or 15 is assigned for each activity that a patient can perform independently. Patients who score 100 on the BI are continent, can feed and dress themselves, get out of bed, walk >1 block, and perform activities of daily living. The mRS is used to measure overall functional disability and handicap after a stroke. The original Rankin scale was modified in 1988 by Warlow et al for the UK-TIA study to accommodate language disorders and cognitive deficits. A score of <2 on the mRS is considered a favorable outcome with minimal or no disability. At screening, a historical BI and a historical mRSS should be obtained from the subject or subject’s caretaker. These determinations should reflect the functional and disability status of the subject before the stroke. These historical determinations do not have to be obtained before enrollment of the subject.

Imaging Evaluation
Imaging techniques such as CT, MRI, and angiography have an important role in screening and monitoring of patients treated with IA thrombolysis, ie, before, during, and after intervention. Imaging evaluates gross anatomic abnormalities, such as the presence of ICH or infarction, as well as vascular perfusion and collateral flow. To reliably evaluate inclusion and exclusion criteria or to assess treatment success, it is important that the imaging examinations be performed according to state-of-the-art technology and are interpreted according to standardized rules.

Angiography
The gold standard for the demonstration of a vascular occlusion in IA thrombolysis trials is angiography. The confirmation of a vascular occlusion seems to be quite important, knowing that up to 20% of patients with suspected cerebral ischemia will have a negative angiogram (possibly due to early spontaneous clot lysis or microvessel occlusion) and another 10% to 20% have other angiographic exclusion criteria.\(^{30,48}\) Also, patients with an acute ischemic stroke might have a variety of arterial occlusion sites despite similar clinical presentations.\(^{30}\)

A complete diagnostic cerebral angiogram of the affected territory should be obtained at baseline. For purposes of investigational trial design, a three or 4 vessel pre-intervention diagnostic cerebral angiogram, including both internal carotid arteries and the dominant vertebral artery, which includes the late venous phase is recommended before thrombolysis to evaluate concomitant pathologies and anatomic variations and to assess collateral flow from all possible sources. In addition, if significant aortic arch disease is suspected, aortic arch angiography should also be performed. Other important parameters to evaluate from a baseline angiogram would be the presence or absence of shunting (appearance of a vein during arterial phase before venous phase) and the presence of a vascular blush, both of which might indicate an increased risk for ICH.\(^{49,50}\)

Location of Occlusion
The proximal extent of occlusion is correlated with technical success of lysis, neurologic recovery, and risk of ICH.\(^{25,26,50}\) The location of occlusion can be reported as described in Table 1.

Perfusion
The Thrombolysis in Myocardial Infarction (TIMI)\(^{51}\) definition was originally adapted and used to describe flow in the coronary arteries from 0 to 3. Its use has been extended to angiographic cerebral blood flow.\(^{14}\) Recently, Thrombolysis in Brain Ischemia (TIBI) definitions have become available from transcranial Doppler data.\(^{52}\) To emphasize the use of a standard grading system for a thrombolytic trial specific to the intracranial cerebral circulation, we propose a Thrombolysis in Cerebral Infarction (TICI) grading system (Table 2).
Collateral Flow
In the absence of direct perfusion, tissue is preserved by the presence of collaterals. Consequently, it is expected that infarct development and the result of thrombolytic drug treatment depend on the presence of collaterals. It has been stated that the presence and size of the ischemic penumbra are influenced by collateral circulation.53 In PROACT-II, for example, the presence of collaterals seemed to have a major effect on the CT appearance of an infarct, as well as on the clinical presentation. Thus, the more collaterals, the smaller was an infarct on CT and the smaller was the stroke scale score. The effect on outcome, however, seemed to depend on treatment as well: in the presence of collaterals, patients treated with IA thrombolysis had a better outcome compared with the control group. In the absence of collaterals, r-proUK did not improve 90-day outcome compared with control. From both outcome and CT data, it was concluded that patients without collaterals might not benefit from drug treatment, whereas patients with collaterals did indeed improve after r-proUK treatment, compared with controls, and that CT findings corroborate the 90-day-outcome result.26 Consequently, it might be important to quantify collateral flow and use this measure in future trials as an inclusion criterion.

The effect of collaterals might also be influenced by location of the occlusion. For example, a proximal MCA clot might occlude the lenticulostriate arteries that supply the basal ganglia and internal capsule. These vessels are not collateralized from the cortex. Therefore, excellent transcortical collaterals might allow cortex to be salvaged, but permanent hemiplegia might still result from infarction of the internal capsule.

In the literature, there is insufficient information on grading systems for collateral flow. The “gold standard” for the assessment of collateral flow is angiography. An estimation of collateral flow was performed in the PROACT-II trial by evaluating the angiographic presence or absence of flow to the ischemic site and to the occlusion site.26 A proper grading of collateral circulation is essential for future clinical trials. We propose that the function of the collateral circulation be evaluated with the grading system shown in Table 3.

Time of collateral filling is somewhat subjective; however, it might be determined by counting the number of frames from contrast-agent filling of the petrous carotid artery (from the anterior circulation) and the proximal basilar artery (in the posterior circulation) to complete collateral filling (provided that the number of frames per second is known, so that the time for collateral filling can be calculated.) This is then compared with time to normal filling of the nonoccluded hemisphere in the parenchymal phase of the angiogram. Slow collateral flow is defined, arbitrarily, as filling that is >2 seconds slower than the contralateral side. Rapid collateral flow is defined as filling that is within 2 seconds of the contralateral side. It is essential that the angiogram include both the arterial and venous phases of the injection to evaluate the collateral pathways.

Computed Tomography
The noncontrast CT scan still is regarded as the most important diagnostic tool in the assessment of patients with a suspected acute stroke54 to exclude hemorrhage and demonstrate early infarct signs. A method of quantifying the volume of early infarct signs from the screening CT scan has been suggested.55 The baseline (screening) CT brain scan should consist of a nonenhanced CT scan with contiguous, discrete (nonhelical) images from the vertex of the calvarium through the foramen magnum. Sections that are 5 mm thick are preferred, but scans should not be thicker than 10 mm. The scan plane should be parallel to the canthal meatal line. Ideally, the screening CT should be performed no longer than 1 hour before initiating thrombolytic therapy. Otherwise, there might be ischemic or hemorrhagic changes that have developed from the time of initial head CT that would have excluded the patient from therapy.

ECASS-I has shown a high rate of protocol violations regarding the baseline CT inclusion criteria. Thus, as implemented in ECASS II, it is recommended that all sites should undergo CT training sessions, so that the reader can detect early CT changes with a high degree of sensitivity and reliability.

Recently, CT scans have been expanded to obtain functional information on the state of the tissue and the location of a vascular clot. As such, CT angiography and a dynamic CT perfusion scan might become part of the screening CT protocol. A CT angiogram, if it can be expeditiously obtained, is recommended to cover the entire cerebrovascular axis, including the anterior (carotid) and posterior (vertebro-basilar) circulation, as well as the extracerebral carotid arteries.56 A helical scan is required for CT angiography; however, multidetector scanners are preferred. Scanning can be performed from the vertex to the aortic arch during the injection of ~100 mL of contrast medium. Vascular opacification can be observed on the cross-sectional images and displayed in 2D and 3D reformations. In the context of controlled, clinical trials of IA thrombolysis, it is possible to validate CT perfusion and CT angiography for the assessment of the tissue and vasculature, in particular, to evaluate and grade the collateral flow. Such a noninvasive, validated screening technique might then in future trials be used to reduce the number of angiograms.

A dynamic perfusion CT scan acquires data at a single location continuously during the transit of a contrast-agent bolus (40 mL) through the tissue.57,58 Reviewing or postprocessing the acquired images allows the assessment of tissue perfusion by virtue of different parameters describing the contrast-agent transit curve. The CT perfusion technique was originally described in the early 1980s59–61 but failed to gain general application. However, newer techniques, in particular, faster scanner generations, and the availability of thrombolytic agents revived interest in CT perfusion imaging.57,58,62–66 The term CT perfusion was initially adopted for the assessment of “perfused blood volume” with contrast-enhanced CT.62 This technique utilizes subtraction images of nonenhanced and contrast-enhanced images of the whole brain, which then indicate the perfused areas of cerebral tissue. After contrast enhancement, Hounsfield units will change in a reference blood vessel, and this allows interpretation of subtraction images, such as maps of fractional, or perfused, blood volume, and therefore, the delineation of an
TABLE 1. Location of Occlusion

- “T” occlusion: embolus to ICA terminus
- Proximal MCA: M1 trunk occlusion at or proximal to the lenticulostrate arteries
- Distal MCA: M1 trunk occlusion distal to the lenticulostrate arteries
- M2: division occlusion beyond the bifurcation of M1
- Vertebrobasilar
- Anterior cerebral
- Proximal ICA occlusion may be present along with an intracranial embolus and should be separately reported.

Acute infarct might be reflected as a reduction in regional cerebral blood volume (rCBV). However, even in an acute ischemic stroke, CBV can be either increased, normal, or decreased, depending on the severity of hypoperfusion and collateral flow.67

Thus, the CT perfusion technique has recently been expanded to assess the whole dynamics of a contrast-agent transit curve (dynamic CT perfusion). Assuming an intact blood-brain-barrier, the contrast agent yields a time-varying change in density or signal intensity. A variety of perfusion indices extracted from the analysis of the contrast-agent transit curve have been proposed based on empirical measures or slightly more sophisticated hemodynamic modeling (eg, arterial deconvolution). Most commonly used are the maximal-density/signal-intensity change (peak), time-to-peak density/signal intensity (TTP), the full width of the contrast-transit curve at half height, or mean transit time (MTT). Integrating the area under the concentration-time curve yields relative estimates of the rCBV, and the ratio of the rCBV and the MTT yields a relative estimate of regional cerebral blood flow (rCBF). Analysis software is commercially available, and algorithms have been developed to actually quantify flow in cerebral tissue.58 In acute ischemia, dynamic CT perfusion has been shown to be a reliable alternative to MR perfusion.63,66,68–70

The presence of collateral flow can be estimated on perfusion imaging by both CT and MR. A typical pattern of collateral flow consists of a lower peak, delayed TTP, increased MTT, decreased flow, and normal or elevated CBF. A typical pattern of absent collateral flow would be characterized by a decreased CBF, which has been shown to indicate a poor prognosis. Moreover, the combination of increased time to enhancement and increased rCBV indicates good collateral flow.

Magnetic Resonance Imaging

An MR brain study at baseline might be performed in addition to or instead of a CT study. However, the same study (CT or MR) should be performed at all scheduled time points. An MRI protocol is suggested to include a T2-weighted or fluid-attenuated inversion recovery sequence, a diffusion-weighted sequence, and a perfusion-weighted sequence. A 3D MRA of the circle of Willis can be performed without (eg, 3D time of flight) or with contrast agent. If a contrast-enhanced gadolinium MRA is performed, care should be taken to acquire the data in the arterial phase of the bolus to prevent venous opacification. MRA demonstrates patency or occlusion of cerebral arteries.

MRI has a high sensitivity and specificity for the diagnosis of ischemic stroke in the first several hours after symptom onset, identifies arterial occlusions, and noninvasively characterizes ischemic pathology.71 Case series have demonstrated and characterized the early detection of intraparenchymal hemorrhage72–74 and subarachnoid hemorrhage75–77 by MRI. Echo planar images, used for diffusion and, in particular, perfusion MRI, are inherently sensitive to the susceptibility changes caused by intraparenchymal blood products.72–74 Consequently, MRI has replaced CT to rule out acute hemorrhage in some centers.

Much attention in recent years has been focused on using MRI for perfusion imaging.29,78–83 On perfusion-weighted imaging the volume of ischemic brain is detected. Contrast-agent transit is observed by using dynamic susceptibility contrast-enhanced T2/T2*-weighted MRI. The same indices used for CT perfusion are used for MR perfusion.

A strong argument for MR perfusion imaging in acute ischemia is the possibility to combine the perfusion information with DWI, a technique that highlights the cytotoxic edema in the core of the infarcted brain. DWI allows detection of cerebral ischemia within minutes of onset, and the temporal evolution of diffusion characteristics enables differentiation of acute from chronic stroke.84 On DWI, the volume of the infarcted lesion appears hyperintense relative to the surrounding tissue. When the region of hyperintensity on DWI is surrounded by a larger perfusion defect, this pattern is called a perfusion/diffusion mismatch.85 This mis-

TABLE 2. Thrombolysis in Cerebral Infarction (TICI) Perfusion Categories

| Grade 0: | No Perfusion. No antegrade flow beyond the point of occlusion. |
| Grade 1: | Penetration With Minimal Perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run. |
| Grade 2: | Partial Perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry into the vessel distal to the obstruction and/or presence of filling from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, eg, the opposite cerebral artery or the arterial bed proximal to the obstruction. |
| Grade 2a: | Only partial filling (<50%) of the entire vascular territory is visualized. |
| Grade 2b: | Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal. |
| Grade 3: | Complete Perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery. |
TABLE 3. Collateral Flow Grading System: Angiographic

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No collaterals visible to the ischemic site</td>
</tr>
<tr>
<td>1</td>
<td>Slow collaterals to the periphery of the ischemic site with persistence of some of the defect</td>
</tr>
<tr>
<td>2</td>
<td>Rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory</td>
</tr>
<tr>
<td>3</td>
<td>Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase</td>
</tr>
<tr>
<td>4</td>
<td>Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion</td>
</tr>
</tbody>
</table>

match indicates the presence of the ischemic penumbra, ie, ischemic tissue at risk that might go on to infarction without revascularization and that is potentially salvageable by flow restoration. MRI thus has tremendous potential for helping direct the treatment of acute ischemic stroke.

However, there are some practical limitations of MRI. Controversy still exists over the pathophysiology of underlying changes in diffusion and the reversibility of changes after reperfusion. It has been advocated to offer studies that take only 10 to 20 minutes to perform, but in reality, an MR examination in an acute stroke patient takes much longer, and sequences are often distorted by motion artifacts and have to be repeated. Patient monitoring is difficult, and the setup is time-consuming. Furthermore, in many institutions, MRI might not be available in an emergency situation.

In experienced centers, a 15-minute MRI session might help select subjects for IA thrombolysis based on a positive diagnosis of an occlusion by MRA or a perfusion defect that exceeds the region of acute injury demonstrated by DWI. Subjects without appropriate pathology on MR images are spared the risk of an unnecessary arteriogram. The combination of DWI and PWI, if it can be obtained in a reasonable time frame, is advocated as a tool in stroke clinical trials and also for assessing the drug effect on ischemic pathology.

Summary
Preprocedure neurologic assessment by a clinician certified in all of the applicable neurologic tests is required at specified time points. The examinations should include the NIHSS, BI, and mRSS assessments. Baseline laboratory studies that should be performed include a complete blood count with platelets, coagulation studies, liver function tests if indicated, and routine electrolyte blood studies.

Baseline imaging studies should include a noncontrast CT head scan and then possibly a CT angiogram, MRI/MRA, perfusion/diffusion imaging studies, and diagnostic angiography as specified in the clinical study protocol. Catheter angiography should include exact information on occlusion location and on collateral flow, which should be evaluated according to a uniform grading system.

Recommendations for reporting include age and gender of the patients enrolled; neurologic deficit baseline NIHSS; functional status by the mRSS and baseline BI; angiographic location, of the clot; baseline perfusion and collateral grade; and CT or MR assessment of baseline hemorrhage and edema. Assessment of perfusion (CT or MR) and diffusion (MR) is optional.

Defining Patient Selection
The selection of the study population should be based on clinical presentation (signs and symptoms of acute stroke presenting in the appropriate time window), CT, MRI, and/or angiography. The entry criteria (ie, inclusion and exclusion criteria) determine which patients will be enrolled into a clinical trial. They also influence patient baseline characteristics. Consequently, the entry criteria influence both clinical outcome and the likelihood of finding a statistically significant effect between treatment arms. The entry criteria used in the previous thrombolytic trials were, in general, based on the same assessment scales, eg, NIHSS score, patient age, noncontrast CT scan, etc. Depending on the drug or device under study, a trial might be designed to avoid enrolling a large population of patients expected to have a very good or very bad outcome regardless of therapy, such as those with mild or very severe strokes. When choosing the specific thresholds for inclusion and exclusion in future trials, it should be recognized that enrolling patients with a relatively high or low chance of having a good outcome might influence the ability of a study to demonstrate a treatment-related benefit, and it might be useful to stratify patients according to variables that predict outcome, such as the NIHSS score. The inclusion and exclusion criteria listed in the following sections have proven useful in several reported major trials of MCA strokes but might not be completely applicable to future trials. For example, recent surgery is listed as a contraindication from previous trials, although a case series showed acceptable risks of cerebral thrombolysis in patients with recent major surgery, including cardiac surgery. Alternatively, some studies might choose to focus on those patients with the most severe strokes with NIHSS scores >25 to 30 or patients with vertebrobasilar strokes whose severity might not be accurately measured with the NIHSS. Therefore, the listed criteria should be tailored according to the design of the individual study.

Inclusion Criteria Used in Prior Trials

Clinical
(1) Age. The recommended minimum age is 18 years (ie, candidate has had his/her 18th birthday). This age is recommended because the legal age to give consent is 18 years or older. An upper limit in prior studies has been recommended to be set at 80 years, mainly because of an increased risk of brain hemorrhage in older patients. However, there might still be clinical efficacy of thrombolysis in older patients. Therefore, for acute stroke trials, it might be suggested to NOT recommend a maximum age, because stroke often affects the elderly population in a much higher proportion. (2) No prior neurologic event that would obscure the interpretation of the signal and current presenting neurologic deficits. (3) Onset of new neurologic signs and symptoms of a stroke within a well-defined time to initiation of treatment. (4) Clinical signs consistent with the diagnosis of ischemic stroke, including impairment of language, motor function, cognition and/or gaze, vision, or neglect. Ischemic stroke is defined as an event
characterized by the sudden onset of a focal neurologic deficit presumed to be due to cerebral ischemia after exclusion of ICH with a baseline CT or MR image. (5) The signal stroke should be (a) acute, (b) the most recent significant, acute worsening of serial neurologic events, or (c) related to a diagnostic radiographic procedure but not an interventional procedure. (6) Minimum NIHSS score >4, except for isolated aphasia or isolated hemianopsia.

CT/MR Imaging

Normal study or early findings that do not meet CT/MR image exclusion criteria (see following sections).

Angiographic

Angiographic evidence of a clot in the vascular distribution consistent with the neurologic deficit. Most likely, this will include the M1 segment or an M2 division of the MCA with complete occlusion (TICI grade 0) or contrast penetration with minimal perfusion (TICI grade 1). Thrombolysis treatment might be expanded to include occlusions of the carotid terminus/ICA, the basilar artery, or their major branches. In addition, inclusion can also be expanded to TICI 2 flow in symptomatic patients in other studies.

Exclusion Criteria Used in Prior Trials

Clinical

(1) Coma (which might be allowed in some posterior circulation protocols). (2) Neurologic signs that are rapidly improving by the time of randomization or treatment. (3) Major stroke symptoms (>25 to 30 on the NIHSS). (4) History of stroke within the previous 6 weeks. (5) Seizure at the onset of stroke. (6) Stroke due to a neurointerventional procedure for treatment of a cerebral aneurysm and/or cerebral arteriovenous malformation (stroke due to diagnostic cerebral angiography or cardiac catheterization might be treated). (7) Clinical presentation suggestive of subarachnoid hemorrhage, even when the initial CT scan is normal. (8) Previous known ICH at any time, neoplasm, and/or subarachnoid hemorrhage. (9) Patients with a known arteriovenous malformation or aneurysm, with or without any evidence of associated hemorrhage. (10) Presumed septic embolus. (11) Presumed pericarditis related to recent acute myocardial infarction. (12) Suspected lacunar stroke. (13) Recent (within 10 to 30 days) surgery, biopsy of a parenchymal organ, or lumbar puncture. (14) Recent (within 10 to 30 days) trauma, with internal injuries or ulcerative wounds. (15) Recent (within 90 days) head trauma. (16) Known active inflammatory bowel disease, ulcerative colitis, or diverticular disease. (17) Any active or recent (within 10 to 30 days) hemorrhage. (18) Known hereditary or acquired hemorrhagic diathesis, eg, aPTT or prothrombin time greater than normal; unsupported coagulation factor deficiency. (19) Baseline laboratory values that suggest prothrombin time greater than normal; unsupported coagulation factor deficiency. (20) Pregnancy, lactation, or parturition within the previous 30 days. (21) Known serious sensitivity to radiographic contrast agents. (22) Other serious, advanced, or terminal illness such that life expectancy is <1 year. (22) Current participation in another research drug treatment protocol. (23) Previous participation in an acute stroke study. (24) Any condition in which angiography is contraindicated. (25) Any other condition that the physician believes would pose a significant hazard to the patient if fibrinolytic therapy were initiated (eg, amyloid angiopathy). (26) Uncompensated hypertension at study entry or hypertension requiring aggressive treatment to reduce blood pressure to nonhypertensive limits. Uncompensated hypertension is defined as systolic blood pressure >180 mm Hg or diastolic blood pressure ≥100 mm Hg on 3 repeated measures at least 10 minutes apart. Aggressive treatment is defined as the need for a continuous, parenteral antihypertensive, such as a nitroprusside drip, or the need to administer >3 doses of a parenteral antihypertensive, such as labetalol.

CT/MR Imaging

Early CT Changes

(1) High-attenuation lesion on CT or corresponding finding on MRI consistent with a hemorrhage of any degree in any location. (2) Evidence of a significant mass effect with a midline shift due to a large infarct. (3) Acute hypodense parenchymal lesion on CT or effacement of the cerebral sulci in more than one third of the MCA territory or suspected stroke region.

Early MR Changes

If screening CT is replaced by screening MR, exclusion criteria comparable to the ECASS criteria have to be defined for MR. Because noncontrast CT and DWI reflect a different physiology, it is not at all justified to replace the established exclusion criterion “presence of CT signs involving more than one third of the MCA territory” to a hyperintensity on diffusion-weighted MR in more than one third or two-thirds of the MCA territory. It is known that diffusion-weighted MR is much more sensitive to early ischemic changes than CT, but it is not known how much diffusion abnormality corresponds to one third MCA pathology on noncontrast CT. This still needs to be defined in a study comparing baseline CT and MR imaging.

Other CT or MR Findings

(1) Evidence of an intracranial tumor (except a small, incidental meningioma). (2) Subarachnoid hemorrhage.

Angiographic

(1) Suspected carotid arterial dissection. (2) Arterial stenosis as the sole lesion or a high-grade stenosis that does not allow safe passage of a catheter. (3) Any nonatherosclerotic arteriopathy (eg, vasculitis). extracranial common carotid artery occlusion, ICA occlusion, including a distal ICA occlusion that extends into the MCA territory, or an anterior cerebral artery occlusion might be defined as an inclusion (see preceding sections) or exclusion criterion, depending on the drug or device studied and the specific study protocol.
Summary
Clinical inclusion and exclusion criteria as well as imaging exclusion criteria are well defined and established from previous IV and IA thrombolytic trials. These criteria should be tailored to the design of the individual study. When screening CT is replaced by screening MR, the exclusion criteria from diffusion-weighted MR still have to be defined. The angiographic inclusion criteria regarding the clot location might vary, depending on the drug or device under study.

Recommendations for reporting include clinical inclusion and exclusion criteria, CT/MR inclusion and exclusion criteria, and angiographic inclusion and exclusion criteria.

Defining Outcome of Therapy
Selection of the primary study end points or outcome measures is among the most important considerations in the design of a phase I, II, or III study. This depends on the expected mechanism and effect of the given therapy, as well as the purpose of the study. There is no perfect outcome measure for acute stroke studies, but there have been several outcome measures that have proved to be quite informative and useful, often used in combination. Because the choice of outcome measures depends on the purpose of a given study, it is helpful to divide the discussion concerning outcome measures into selection of end points for phase I and II studies and outcome measures for phase III or pivotal studies.

Phase I
The primary goals of a phase I study are choice of drug dose (if the intervention is a medication) and initial investigation of a therapy’s safety in humans at the chosen dose. A phase I study is not designed to test efficacy. Selection of outcome measures should reflect concerns of safety. Because most clinical trials are primarily concerned with recanalization strategies, the safety measures should reflect potential side effects of recanalization agents or strategies. The 2 primary safety outcome measures for acute stroke studies of recanalization are mortality and ICH, particularly hemorrhage that causes clinical deterioration. All recanalization strategies to date have been associated with ICH including thrombolytic agents, antithrombotic therapies such as heparin, defibrinogenating agents such as Ancrod, glycoprotein (GP) IIb/IIIa platelet-receptor blockers, and mechanical recanalization strategies. Other major safety concerns include nonintracranial bleeding that requires transfusion or surgical treatment, particularly bleeding due to puncture of the femoral artery.

One of the difficulties in phase I studies is determining whether the incidence of serious adverse events, such as death or symptomatic ICH, is above the level expected for a given patient population. For example, the risk of death and symptomatic ICH increases dramatically with the severity of the baseline clinical stroke as measured by the NIHSS.36 In the NINDS t-PA Stroke Trial, persons with an NIHSS >20 had a 17% risk of symptomatic ICH compared with persons with an NIHSS ≤20 who had an overall risk of ≤5%. Phase I studies involving cerebral recanlization that enroll the most severe stroke patients will thus expect to have a higher rate of symptomatic ICH than recanalization studies in which the overall severity of the patients is less. Thus, a recanlization study with a patient population with a median NIHSS of 20 at baseline would be expected to have a higher rate of symptomatic ICH (at least 10% to 12%) compared with the NINDS t-PA Stroke Trial of IV tPA, wherein the median NIHSS was 14 and the overall rate of symptomatic hemorrhage was 6.4%.7

The design of phase I studies should focus on stopping rules based on substantial deviations above the expected rate of death or symptomatic ICH for the population under study. Comparison with previous studies with similar related design and similar populations can be helpful in planning the projected sample needed to assess the safety of a given technique. For some interventions designed to improve the safety profile, the expected rate from previous studies might be unacceptably high and the stopping rule might be based on a lower value.

Phase II
Besides providing additional data concerning safety, phase I and particularly phase II studies provide an opportunity to gather data regarding potential measures of drug activity and/or device efficacy in a patient population that is similar to that proposed for the large-scale efficacy or phase III study. Phase I and II studies should help to screen out therapies that should not be taken to phase III and should provide the data needed to develop sample size estimates for a phase III pivotal trial.

Ideal study end points and outcome measures should be easy to measure, reproducible, valid, clinically meaningful, and resistant to bias.93 Outcome measures should also detect clinically relevant differences between various therapies for a given disease with the smallest number of patients possible. For a phase II study, one would like to rule out therapies with a high probability of being ineffective by treating a few patients as quickly as possible.

End points for activity or efficacy in phase II trials might be selected on the basis of previously positive studies, such as the NINDS t-PA Stroke Trial. However, some phase II studies have used nonclinical end points, such as surrogate outcomes that were anticipated to correlate with important clinical results.

There are currently no positive neuroprotective trials to provide such information for future planned neuroprotective trials. Only the PROACT-II study provides some data regarding end points for IA recanalization.14 Information about placebo-treated patients from similar, previously reported acute stroke trials should be pooled to obtain patients with similar severity of stroke, demographics, etc. Such a pooled-group can be useful for comparison with patients treated in a phase I or II acute stroke trial but is not recommended for phase III randomized trials.

Phase III
Outcome measures or end points for efficacy in phase III trials should be based on the selection of end points from phase II studies as well as previously performed similar phase III studies of acute ischemic stroke, if available. In contrast to a phase II study, wherein one wants to rule out potentially ineffective treatments with the smallest number of patients
possible, the purpose of phase III studies is to demonstrate a clinically significant difference in efficacy (generally functional long-term outcome), easily recognized by physicians as well as patients. Phase III studies often contain many ancillary secondary end points, including imaging end points. If these secondary end points are all positive and in the same direction as the primary end point, then they can greatly strengthen the results of a study. However, these secondary end points alone are generally not sufficient to demonstrate efficacy as determined by the FDA. Success in a secondary outcome, in the absence of success in a primary outcome, would be considered hypothesis generating and would generally require at least 1 additional phase III study to verify the result.

There are 2 major types of outcome measures for acute stroke studies: clinical outcome measures and radiographic measures. Clinical outcome measures include neurologic impairment scales, disability measures, and handicap scales. Examples of neurologic impairment scales include the NIHSS, Canadian Neurologic Scale, and Scandinavian Stroke Scale. These scales might be the most sensitive to change and have the greatest capacity to differentiate between treatment groups, making them particularly useful for phase II studies. Disability and handicap scales include such scales as the BI, Rankin, and Stroke Impact Scale. Handicap and disability scales are generally not the primary outcome measures in phase I and II trials but should always be included in these earlier studies to provide information used in designing the phase III trial and to provide data for comparing the new treatment to previous studies. Scales assessing the quality of life after stroke, such as the EuroQol, have been used little in previous phase III studies, although are becoming part of most current designs of acute stroke trials.

If the treatment is expected to influence only 1 aspect of poststroke impairment, the primary outcome measure for the phase III trial might be chosen accordingly. Although 1 outcome might be chosen as primary, it is also important to collect data on outcomes describing the multiple dimensions of poststroke impairment so that the full range of treatment benefit and harm can be understood and compared with previous studies. Currently, the most successful long-term, functional end points have been a Rankin of 0 to 1 and a Rankin of 0 to 2. The choice of outcome measure will depend, in part, on the expected magnitude of the beneficial effect of the treatment.

Comparison of end points in the ECASS-II, PROACT-II, and NINDS t-PA Stroke Trial illustrates how selection of an end point depends on the expected action of the drug. In the NINDS t-PA Stroke Trial, in which patients were treated within 3 hours, a Rankin of 0 to 1 at 3 months was the third most sensitive end point with regard to long-term efficacy. Using this end point would require only 91 patients per treatment group to detect a benefit for tPA-treated patient was demonstrated. The PROACT-II study was an IA study that also treated patients within 6 hours and found that a Rankin of 0 to 2 was a more sensitive measure of drug treatment benefit than a Rankin of 0 to 1.

The different sensitivities of different end points for the Rankin scale are consistent with the biology of acute ischemic stroke. Interventional thrombolytic therapy administered soon after the onset of cerebral ischemia should be more likely to open the occluded artery and to salvage more viable brain tissue than recanalization at a later time point, by which there has already been more extensive tissue damage. Thus, patients achieving earlier recanalization would be more likely to return to normal or near normal as measured by a Rankin of 0 to 1. Patients treated after 3 hours of symptom onset would be less likely to have sparing of brain but might still accrue some benefit. Such patients would be less likely to be returned to a Rankin of 0 to 1 but might have a shift in their disability to a Rankin of 0 to 2. It is likely that for later recanalization studies (>3 hours), a Rankin of 0 to 2 might be a better long-term outcome measure than a Rankin of 0 to 1, whereas earlier recanalization studies at <3 hours might find the Rankin of 0 to 1 a more powerful measure. Dichotomized end points (eg, Rankin 0 to 1, 0 to 2, etc) are not the only valid manner to analyze outcome scales. Use of the full scale (eg, in a rank sum analysis) is an equally valid manner to analyze outcome assessments, which might offer certain advantages and should also be considered.

The other major category of end point assessment is the radiographic measurement of ischemic damage or activity. The most-utilized radiographic end point has been the measurement of infarct size on a CT scan at a predefined time after stroke onset. Other exploratory radiographic end points include measurement of cytotoxic edema on diffusion MR or a measure of the mismatch between diffusion abnormalities and hypoperfusion abnormalities on MRI (diffusion/perfusion mismatch). For thrombolytic therapy or mechanical recanalization strategies, angiographic findings or transcranial Doppler ultrasound might provide surrogate markers of in vivo drug or mechanical reperfusion activity. However, because improvements in radiographic measures are not always correlated with improvements in poststroke clinical impairment, radiographic measures of recanalization should be viewed as surrogate markers and not as primary outcome measures. The ideal surrogate marker is an indicator of biologic activity that is related to the measurement of functional outcome in a patient. Ideal surrogate measures should be easy to perform and reproducible, should be observable over a short time frame, should not interfere with other necessary treatments or assessments, and should be more sensitive to changes induced by the therapeutic intervention than functional outcome.

PROACT-I and II provide good examples of the use of surrogate outcomes in a phase II and phase III trial. In the PROACT-I study, recanalization of the main MCA, M1, and M2 segments 2 hours after initiating drug treatment was the primary end point of the study and a surrogate marker for
activity of the drug. The PROACT-I study did demonstrate that IA recombinant pro-UK plus heparin was more effective in reopening the artery than heparin alone. The use of this surrogate end point also demonstrates a potential problem with surrogates, in that recanalization rates at delayed time periods might not be correlated at all with clinical outcome if infarction has already occurred. Although demonstration of angiographic recanalization is a helpful surrogate in IA studies, it might not be equivalent to demonstration of brain salvage and improved functional outcome.

Finally, other markers of ischemic activity in the brain can be plasma levels of various substances that are released into the circulation from the injured brain. These can include substances such as neuron-specific enolase, S-100, thrombomodulin, etc. These outcome measures are in the experimental phase and have not been used successfully as surrogate markers in a phase II or III study at the present time.

The most powerful measure for a phase I or II recanalization study could be either a clinical or radiographic measure, but the only successful end points thus far in an acute stroke trial are clinical end points. Measurement of the volume of cerebral infarction with CT at 24 hours or at 3 months was not as powerful as the clinical end points in the NINDS t-PA Stroke Trial or the PROACT studies, even though the effect in the CT end point in the NINDS t-PA Stroke Trial was in the same direction. The reasons for the relative lack of sensitivity of CT imaging end points are complicated but point out potential limitations of imaging end points in general.

Statistical Approaches
Two statistical approaches have recently been proposed as a means to increase the power of phase II and III studies. First, a global clinical end point, which is a statistical measure that uses 2 or more end points, has been found to be a more powerful measure of drug efficacy than the individual end points themselves. Part of the advantage of the global measure is that “there is no one perfect stroke outcome measure that measures all areas of clinical relevance.” For example, a global outcome measure that was used in the NINDS t-PA Stroke Trial looked at the effect of tPA across 4 related but separate clinical end points: the NIHSS score, the Rankin score, the BI, and the Glasgow Outcome Scale. In the NINDS t-PA Stroke Trial, the global outcome measure was more powerful than the individual end points in this trial. Retrospectively, the global outcome method was also applied to the ECASS-I study, which was a negative study as judged by its primary end point, but gave a positive result when global outcomes were used. The global outcome approach assumes a common dose effect among the outcome measures used. If 1 outcome measure is positively affected by therapy, and all other outcome measures worsen, a test of the single, positively affected outcome will be more powerful than the global approach. If all outcome measures are positively affected by therapy and affected by about the same amount, the global test will be more powerful than any of the outcomes used alone.

Another statistical approach to find more powerful end points for phase II and III studies has been to explore existing databases of positive studies. The NINDS tPA study group recently reported use of the classification and regression tree (CART) methodology. The CART method examines only possible binary cut points, for example, comparing the median NIHSS score in 2 treatment groups at 24 hours, and does not evaluate other nonbinary end points. Binary end points work best when outcome measures are not distributed normally but are clustered at high and low values (U- or J-shaped distributions), as are often observed in stroke trials. The distributions of measures of outcome after stroke with the use of treatment measures such as the BI and volume of infarction are generally J-shaped. Thus, the CART method can be a useful tool to explore clinical and radiographic end points in acute stroke studies. This method attempted to find the measure or measures, of all possible clinical or radiographic measures, that best separated the treatment groups in the NINDS trial.

Based on the CART analysis of the NINDS t-PA Stroke Trial, 4 of the 5 most powerful end points in detecting early activity of tPA (24 hours after onset of therapy) involve the NIHSS score. With these outcome measures, the projected sample sizes would be 60 to 100 per patient treatment group. For the end point at 3 months, the functional measure of a Rankin score of 0 to 1 and measures with the NIHSS score were the most sensitive measures of long-term efficacy of rtPA. These different analytical methods demonstrate that there are a variety of ways to analyze data and that all possible analytical methods should be considered before analyzing the complete data obtained on patient outcome. Possible outcome variables chosen for a study include measures of both efficacy and safety. Suggestions for these outcomes to be measured are listed in the next section.

Efficacy Variables
Primary Variable
The choice of the primary efficacy variable depends on the phase of the clinical trial. As such, in a phase I or II trial, a suggested primary efficacy end point might be the TICI 2 or 3 perfusion of the previously occluded artery, based on angiographic assessment of predefined time points, eg, 60 or 120 minutes after treatment initiation. For a phase III trial, a suggested efficacy end point would be the percentage of subjects achieving an mRSS ≤1 or 2 at 90 days after therapy.

Secondary Variables
Secondary variables include the following: (1) The NIHSS score at 90 days. (2) The BI at 90 days. (3) Mortality at 90 days. (4) For a phase III trial, recanalization at a defined time point (eg, 60 or 120 minutes) after initiation of drug infusion (or randomization for control patients) as assessed with the TICI grading system. (5) For a phase I or II trial, an mRSS at 90 days. (6) Economic impact, as determined by length of initial hospitalization and discharge status through 90 days. (7) Total quality-of-life scores at 90 days, as measured by general and stroke-specific subject questionnaires. (8) Infarct volume on CT or MR images at defined time points (eg, 24 hours, 7 to 10 days, 30 days, 90 days) after treatment initiation.
Safety Variables (see Complications Section)

Primary Variable
The primary safety variable is suggested to be ICH causing neurologic deterioration within 24 to 36 hours after randomization, as determined by an independent examiner. In general, an increase of the NIHSS \( \geq 4 \) should be considered significant.

Secondary Variables
Secondary variables include the following: (1) Incidence and severity of nonintracranial bleeding complications. (2) Incidence and severity of nonhemorrhagic adverse events. (3) Changes in laboratory parameters (hematology and clinical chemistry) from baseline to specified posttreatment determinations. (4) Incidence of transfusion of blood and blood products. (5) Incidence and severity of procedural complications related to cerebral angiography and IA infusion of the thrombolytic agent. (6) In the case of a device study, technical complications or vascular damage at the target lesion such as perforation or dissection.

Summary
In conclusion, selection of outcome measures for recanalization studies of acute ischemic stroke is critical and should depend on the type of study, purpose of study, and expected action of the therapy. Currently, there is no perfect outcome measure for acute stroke studies, but outcome measures that use a combination of end points and outcome measures that have been positive in previous recanalization studies might be the preferred choice. If a single primary outcome measure is chosen, it is important to collect data on outcomes that measure other aspects of poststroke impairment so that the new therapy can be compared with other treatments.

Recommendations for reporting include the primary efficacy variable, secondary efficacy variables, primary safety variable, and secondary safety variables.

Treatment Description
Treatment description includes techniques of angiography, thrombolysis, anticoagulation, and patient management in the immediate treatment period.

Angiography
In patients with appropriate clinical and CT criteria, a complete cerebral arteriogram (both carotids, I or both vertebral arteries, and possibly, arch study) should be obtained to evaluate the site of vessel occlusion, extent of thrombus, number of territories involved, and collateral circulation, as described in the section on pretreatment evaluation. In addition, angiography should also be used to assess and determine clot volume and clot burden before treatment. Cerebral angiography should be repeated at defined time points (eg, every 15 minutes to 60 minutes and/or 120 minutes after initiation of thrombolysis, unless complete recanalization occurs sooner). The angiogram should be obtained with the same catheter position, contrast injection volume and rate, and angiographic views before, during, and after the procedures to adequately assess the results of therapy.

After angiography and treatment, if indicated, the femoral arterial site might be closed with an FDA-approved closure device, or hemostasis might achieved by manual compression, as per institutional protocol. Alternatively, a sheath can be left in place until it is thought safe to remove at a later time when the patient is more stable.

A Core Neuroradiology Facility should assess the angiograms and categorize subjects as complete responders, partial responders, or nonresponders for the outcomes of recanalization and restoration of distal flow (as defined subsequently). This is recommended to minimize variability in reporting.

General Recommended Technique of IA Thrombolysis
After the diagnostic angiogram is obtained, a guide catheter is placed in the parent artery of the target lesion. After confirmation of the intracranial occlusion site and documentation of TICI flow, the microcatheter is guided to the site of vessel occlusion. Variations in therapeutic technique include traversing the occlusion and lacing the clot with drug, embedding the microcatheter in the occlusion, or simple proximal infusion. Institution of therapy might be with or without initial bolus and should be recorded as such.

Many variations in catheter design and delivery technique have been described.\(^9\) Two types of microcatheters are being used most often for local cerebral thrombolysis, depending on the extent of clot formation. For the majority of IA cases, a single end-hole microcatheter is used, whereas for longer segments of clot formation, multiple side-hole infusion microcatheters might be used. Superselective angiography through the microcatheter might be performed at regular intervals to assess the degree of clot lysis and to adjust the dosage and volume of the thrombolytic agent.

A superselective angiogram might be obtained at specified time periods during the procedure through the infusion microcatheter or through the guide catheter, and if there is partial clot dissolution, the microcatheter might be advanced into the remaining thrombus, where additional thrombolysis is performed. As the thrombus is dissolved, the microcatheter is advanced into more distal branches of the intracranial circulation up to the M2 segments, so that the majority of the thrombolytic agent enters the occluded vessel and is not washed preferentially into adjacent open blood vessels. Recanalization can be achieved up to the specified time period for drug infusion after the procedure begins. The goal is to achieve rapid recanalization with as little thrombolytic agent as possible, to limit the extent of brain infarction, and to reduce the risk of hemorrhage.

The effect of recanalization on angiographic perfusion should be reported with the TICI grading system. Subjects can be categorized as complete responders (TICI 3), partial responders (TICI <3 but \( \geq 1 \) category improvement from baseline), and nonresponders (no improvement in TICI category). The time from symptom onset to start of thrombolysis should be reported.

Thrombolytic Agent
The various thrombolytic drugs currently reported include recombinant tissue plasminogen activator (rtPA), urokinase
(UK), single-chain urokinase plasminogen activator (scu-PA or pro-UK), recombinant pro-urokinase (r-pro-UK), streptokinase (SK), acylated plasminogen SK activator complex, reteplase, and tenecteplase (TNK).100–107 These thrombolytic agents differ in stability, half-life, and fibrin selectivity. UK and SK are nonfibrin-selective and therefore can result in systemic hypofibrinogenemia, whereas tPA and r-pro-UK are fibrin selective and are only active at the site of thrombosis.108–111 The arginine buffer that is mixed with the tPA preparation can potentially block the binding site for fibrin and theoretically decrease the efficacy of IA tPA compared with IV tPA.103,109–115 r-pro-UK is not taken up by platelets, is promoted by a different fibrin fragment than tPA, and in coronary patients has a low rate of reocclusion. However, r-pro-UK does require heparin for maximal thrombolytic effect.13,14,112 Newer agents such as reteplase and TNK-tPA are even more fibrin-specific but have not been tested in acute stroke in controlled, clinical trials. Despite these differences, with some drugs having theoretical advantages over others, it remains to be proven whether 1 thrombolytic agent is superior to another in terms of safety and efficacy in acute ischemic stroke. Therefore, the results of PROACT-I and II might not be applicable when agents other than r-pro-UK are used for IA thrombolysis.

Administration of the thrombolytic agent should be reported as drug concentration, total volume infused, total amount of drug given, infusion time, rate of infusion, and total elapsed time. Total elapsed time should be defined as the time from the start of the first infusion to the end of the last infusion. Other ancillary maneuvers such as clot penetration, mechanical disruption, use of clot retrieval devices, angioplasty of occlusion, hydrolyzers, ultrasound lysis augmentation, etc., should be recorded. A suggested protocol from the Interventional Stroke Therapy Outcomes Registry (INSTOR [www.strokeregistry.org]) for recording these drugs and devices is suggested in Table 4.

Adjuvantive Therapy

Once a site of vascular occlusion that corresponds to the patient’s neurologic deficit is angiographically confirmed, IV heparin is given by most neurointerventionalists. Systemic anticoagulation with heparin reduces the risk of catheter-related embolism. Also, the thrombolytic effect of some agents such as r-pro-UK is augmented by heparin. Another rationale for antithrombotic therapy is prevention of acute reocclusion, which is more common with atherothrombosis than with cerebral embolism. These indications are counterbalanced by the potentially increased risk of brain hemorrhage when heparin is combined with a thrombolytic agent.

There is no standard heparin regimen established for IA thrombolysis in acute stroke. This is dependent on the thrombolytic agent used and the catheter techniques employed. Some neurointerventionalists use weight-adjusted heparin, which keeps the activated clotting time (ACT) between 200 and 300 seconds. PROACT-I113 reported a 27% rate of symptomatic brain hemorrhage when a conventional heparin regimen (100 U/kg bolus and 1000 U/h for 4 hours) was used with IA r-pro-UK. Subsequently, a standard low-dose heparin regimen was used (2000 U bolus and 500 U/h for 4 hours), which reduced the symptomatic brain hemorrhage rate with IA r-pro-UK to 7% in PROACT-I and to 10% in PROACT-II. This dose of heparin does not prolong the aPTT in most patients. On the basis of the PROACT trials, many neurointerventionalists now use a low-dose heparin regimen during IA thrombolysis.

GP IIb/IIIa inhibitors have never been studied in a randomized trial of IA thrombolysis in acute stroke. The potent GP IIb/IIIa platelet inhibitor abciximab (Reopro, Centocor) has been used successfully instead of heparin in patients undergoing acute or elective cerebrovascular interventions.116 Coronary doses of IV abciximab appear to be safe in patients with acute ischemic stroke up to 24 hours after onset.117 GP IIb/IIIa agents might be most efficacious when the risk of acute reocclusion is great, such as in basilar artery atherothrombosis.118 The safety and efficacy of GP IIb/IIIa agents in patients with embolic occlusion of cerebral vessels, which is the usual cause of MCA occlusion, is less clear.

Blood Pressure Management

Blood pressure should be monitored continuously, ie, no less frequently than every 60 minutes and initially every 15 minutes for 24 hours in an intensive care unit setting. The blood pressure is recommended to be monitored at least every 6 hours during the next 5 days, beginning after the initial 24-hour period. Should the blood pressure exceed 170 to 180 mm Hg systolic or 100 to 110 mm Hg diastolic, appropriate measures to control blood pressure should be instituted. Target blood pressure values are ≤160 mm Hg systolic and ≤90 mm Hg diastolic in the otherwise nonhypertensive subject. Discretion, careful monitoring, and management are required.

Vital Signs (Pulse and Respiration Rate)

Pulse and respiration rates should be continuously monitored every 60 minutes during the first 24 hours after the completion of the study drug infusion and, if stable, every 6 hours during the next 5 days, beginning after the initial 24-hour period. Each subject should be closely watched for clinically significant changes in neurologic and/or functional status.

Summary

Standardization of intraprocedural techniques for performance of diagnostic cerebral angiography and all therapeutic procedures should be strictly followed to decrease as many technical variables that might potentially confound outcomes. Adjunctive therapy (including periprocedural and postprocedural drugs and antiplatelet medications), other physiologic parameters (such as blood pressure control), and follow-up imaging studies should also be uniformly standardized and strictly adhered to.

Recommendations for reporting include the following: (1) Technique of angiography. (2) Time from symptom onset to start of thrombolysis. (3) Technique of thrombolysis (drug or device used, volume and total amount of drug, infusion time and rate, elapsed time, number of device activations). (4) Use of adjunct medications (ie, anticoagulants, antiplatelets). (5) Final angiographic perfusion grade at a defined time. (6) Blood pressure targets and management.
<table>
<thead>
<tr>
<th>Interventionsal Stroke Therapy</th>
</tr>
</thead>
</table>
| Microcatheter type:           | ○ End-hole  
|                               | ○ Multiside-hole  
|                               | ○ Intime  
|                               | Other, specify: ___  
| Was IV bolus given?           | ○ Yes ○ No  
| What bolus was given?         | Alteplase (Activase) __ mg U  
|                               | Reteplase (Retavase) __ mg U  
|                               | Tenecteplase (TNKase) __ mg U  
|                               | Abciximab (ReoPro) __ mg U  
|                               | Other: ___ mg U  
| Was an infusion given?        | ○ Yes ○ No  
| What infusion was given?      | Alteplase (Activase) __ mg U  
|                               | Reteplase (Retavase) __ mg U  
|                               | Tenecteplase (TNKase) __ mg U  
|                               | Abciximab (ReoPro) __ mg U  
|                               | Other: ___ mg U  
| Date and time of start of intravenous fibrinolysis | ___/___ ___:___ NA  
|                               | (MM/DD/YYYY HH:MM)  
| Date and time of interventional stroke therapy | ___/___ ___:___ NA  
|                               | (MM/DD/YYYY HH:MM)  
| Initial catheter location:    | ○ 1=Internal carotid of the cervical carotid bifurcation  
|                               | ○ 2=Distal internal carotid  
|                               | ○ 3=Origin M1  
|                               | ○ 4=Mid M1  
|                               | ○ 5=M1 bifurcation  
|                               | ○ 6=M2 upper/anterior division  
|                               | ○ 7=M2 posterior/angular division  
|                               | ○ 8=A1 proximal anterior cerebral artery  
|                               | ○ 9=A2  
|                               | ○ 10=Distal vertebral artery proximal to PICA  
|                               | ○ 11=Distal vertebral artery at vertebrobasilar junction  
|                               | ○ 12=Proximal basilar artery  
|                               | ○ 13=Distal basilar artery  
|                               | ○ 14=P1 proximal posterior cerebral artery  
|                               | ○ 15=P2  
| Was the occlusion able to be traversed by a guidewire? | ○ Yes ○ No  
| Was the occlusion able to be traversed by the catheter? | ○ Yes ○ No  
| Was antegrade flow improved by traversing the occlusion with the catheter? | ○ Yes ○ No  
| TICI score:                   | ○ 0. No flow past occlusion  
|                               | ○ 1. Minimal penetration distal to obstruction with no perfusion of distal territory  
|                               | ○ 2. Distal perfusion of brain present, but either to only a partial territory or with inadequate perfusion  
|                               | ○ 3. Complete and normal distal perfusion  
| Was any device used to perform mechanical clot disruption (all that apply)? | ○ Neuro-jet  
|                               | ○ Thrombectomy device  
|                               | ○ Balloon  
|                               | ○ Snare  
|                               | ○ Guidewire manipulation  
|                               | ○ Catheter manipulation  
|                               | ○ Balloon angioplasty  
|                               | Other: ___  

*TABLE 4. Protocol for Recording Treatment From Intervventional Stroke Therapy Outcomes Registry*
Posttreatment Evaluation: Functional Status and Duration of Follow-Up

After randomization, all subjects should be followed up for all end points, if possible, regardless of clinical outcome, for at least 90 days. Quality-of-life data should also be obtained at hospital discharge (ie, 7 to 10 days) and at the 90-day visit. Posttreatment evaluation includes scheduled clinical, neurologic, and radiologic assessments. The most important are described below.

Cerebral CT or MR Images
Noncontrast cerebral CT or MR imaging should be performed at defined time points after initiation of randomized therapy. Most commonly, the time points at 24 hours, 7 to 10 days, 30 days, and 90 days are used for IV and IA trials. For comparisons with already performed and published trials, similar time points are recommended. In the event of abrupt neurologic deterioration or when deemed necessary by the investigator, emergency cerebral CT or MR imaging should be performed. An immediate evaluation of the presence/absence of hemorrhage, edema, and/or infarction as contributors to the clinical deterioration should be made. Cerebral hemorrhage is categorized as hemorrhagic infarct or parenchymal hematoma by the following definitions8,9: Hemorrhagic infarct is any area of petechial or small, confluent hemorrhages within larger regions of hypodense, ischemic injury without mass effect. A parenchymal hematoma is more homogeneous areas of hemorrhage, with or without intraventricular extension, usually with mass effect.

Hemorrhage
Subjects should be carefully monitored throughout hospitalization for clinical indications of hemorrhage, both intracranial and peripheral. In the event of a significant hemorrhage, additional hemoglobin determinations must be obtained to classify the severity of the bleeding complication as well as to follow the event until it stabilizes.

Neurologic Evaluations
Repeated NIHSS determinations should be performed just after the final angiogram and at defined time points after treatment (eg, at 24 hours, 72 hours, 7 to 10 days, 30 days, and 90 days). An additional NIHSS score should be obtained when any signs of neurologic deterioration occur or in the event of an ICH to assess neurologic deterioration.

Neurologic evaluations through 72 hours can be performed by any physician or research nurse certified in administering the evaluations via the NIHSS training tapes. It is not necessary that this examiner be a neurologist or be blinded to subject treatment assignment or angiographic outcome. For randomized trials, neurologic evaluations at 7 to 10 days, 30 days, and 90 days are recommended to be performed by certified examiners who are blinded to the subject’s angiographic outcome and treatment group. The same blinded examiner should perform all follow-up evaluations on a given subject.

Disability Outcomes
Functional (disability) outcome should be assessed with the mRSS and the BI for activities of daily living at 7 to 10 days, 30 days, and 90 days by the same blinded neurologist who performed the NIHSS evaluations at these time periods. The examiner must be certified in administering the BI by means of a written examination.

Quality of Life
Quality of life should be assessed at 90 days. Although this has not been commonly performed in prior stroke studies, it is becoming part of most current designs of acute stroke trials. The EuroQol scale is being commonly used.

Summary
Posttreatment evaluation including written documentation of vital signs with accurate blood pressure monitoring, pulse, and respirations is needed. Standardized follow-up imaging with CT, MR, and angiography is required for all patients to assess the degree of ischemic brain damage and angiographic recanalization.

Disability outcomes measured by the NIHSS, mRSS and BI and disability outcomes assessment are required. These should be performed by the same certified neurologist who has been blinded to the randomization of the patient at 30 and 90 days after treatment.

Recommendations for reporting include (1) follow-up CT/MR results; (2) neurologic deficit at 90 days on the NIHSS; (3) functional status at 90 days on the mRS and BI; and (4) quality of life at 90 days on the EuroQol or other comparable scale.

Complications and Adverse Events
The physician investigator should monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The physician investigator should assess and record any adverse event in detail on the adverse event case report form (CRF), including the date of onset, description, severity, intermitteness, duration and outcome, relation of the adverse event to study drug or control, relation of the event to procedure (cerebral angiography or IA infusion), an alternative etiology for events not considered “probably” related to study treatment, and any action(s) taken. For adverse events to be considered intermittent or continuous, the events must be of similar nature and severity. Adverse events, whether in response to questioning, observed by site personnel, or reported spontaneously by the subject, should be reported on the appropriate CRF.

Adverse Event
An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject, irrespective of causal relation with the procedure or treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a therapeutic (investigational) product (drug or device), whether or not the event is considered causally related to the use of the product. The definitions described subsequently for serious adverse events and for the severity of adverse events have been previously accepted by the FDA for regulatory analysis in prior trials. However, alternative ways to summa-
rize the data for publication, rather than for regulatory approval, can use other definitions, such as those already published in prior Society of Cardiovascular and Interventional Radiology documents and guidelines (Table 5).

**TABLE 5. Definitions of Complications**

<table>
<thead>
<tr>
<th>Minor complications</th>
<th>Major complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. No therapy, no consequence</td>
<td>C. Require therapy, minor hospitalization (&lt;48 hours)</td>
</tr>
<tr>
<td>B. Nominal therapy, no consequence; includes overnight admission for observation only</td>
<td>D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (&gt;48 hours)</td>
</tr>
<tr>
<td></td>
<td>E. Permanent adverse sequelae</td>
</tr>
<tr>
<td></td>
<td>F. Death</td>
</tr>
</tbody>
</table>

*See www.strokeregistry.org

Such an event can result from use of the drug or device as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a preexisting condition or illness is considered an adverse event. Worsening of neurologic status for IA lysis is defined as an increase in NIHSS by ≥4. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

For an IA thrombolytic study, the term adverse event encompasses both hemorrhagic as well as nonhemorrhagic events, including events related to the protocol procedures of cerebral angiography and IA infusion of the thrombolytic agent.
Serious Adverse Events

Serious adverse events are defined as follows. Protocols will usually require that serious adverse events be reported to the sponsor or the sponsor’s designate within 24 hours of occurrence or notification of the site: (1) Death: an event that results in the death of a subject. (2) Life-threatening: an event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. (3) Inpatient hospitalization: an event that results in admission to a hospital for any length of time. This does not include an emergency department visit or admission to an outpatient facility. (4) Prolongs hospitalization: an event that occurs while the study subject is hospitalized and prolongs the subject’s hospital stay. (5) Persistent or significant disability/incapacity: an event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance, such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle). (6) Important medical event requiring medical or surgical intervention to prevent serious outcome: an important medical event that, based on medical judgment, might not be immediately life-threatening or result in death or hospitalization but that might jeopardize the subject and might require medical or surgical intervention to prevent any of the outcomes listed previously (ie, death, life-threatening, inpatient hospitalization, prolongation of existing hospitalization, congenital anomaly/birth defect, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Although pregnant subjects are likely to be excluded from enrollment in a trial, both spontaneous and elective abortions will be reported as serious adverse events.

Severity

Severity of Nonhemorrhagic Adverse Events

The investigator should use the following definitions to rate the severity of each nonhemorrhagic adverse event: (1) Mild: The adverse event is transient and easily tolerated by the subject. (2) Moderate: The adverse event causes the subject discomfort and interrupts the subject’s usual activities. (3) Severe: The adverse event causes considerable interference with the subject’s usual activities and might be incapacitating or life-threatening.

Note that a severe adverse event is not necessarily serious by regulatory definition. The term “severe” is a measure of intensity, whereas the term “serious” is assigned on the basis of the regulatory criteria discussed previously.

Severity of Hemorrhagic Adverse Events

Severity of hemorrhagic events are categorized according to a standard classification as follows: (1) Major hemorrhagic event: any hemorrhagic event directly resulting in death; any ICH; any retroperitoneal hemorrhage; overt bleeding associated with a need for transfusion of 2 or more units of blood or which requires surgical intervention; overt bleeding associated with a decrease from baseline in hemoglobin of at least 2.0 g/dl.

Symptomatic Hemorrhagic Event

A symptomatic hemorrhagic event is any intracerebral bleeding causing neurologic deterioration (increase in NIHSS by ≥4).

Minor Hemorrhagic Event

A minor hemorrhagic event is any overt bleeding that does not meet the criteria for major bleeding.

To ensure consistent reporting of the severity of hemorrhagic complications, documentation of pre-event and postevent hemoglobin values are required. Hemoglobin values are to be monitored until stabilized, and all values are to be recorded in the CRF. For subjects with severe bleeding complications, volume replacement by administration of cryoprecipitate, fresh frozen plasma, or packed red blood cells, as appropriate, should be considered.

Relation to the Study Drug

The investigator should use the following definitions to assess the relation of the adverse event to the use of the study drug. “Study drug” in any trial includes both the drug and/or technique under investigation and the protocol-mandated control group. (1) Probable: An adverse event has a strong temporal relation to the study drug or recurs on rechallenge, and another etiology is unlikely or significantly less likely. (2) Possible: An adverse event has a strong temporal relation to the study drug and an alternative etiology is equally or less likely, compared with the potential relation to the study drug. (3) Probably not: An adverse event has little or no temporal relation to the study drug, and another etiology exists. (4) Not related: An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (eg, has no temporal relation to the study drug or has a much more likely alternative etiology).

The definitions for relations of bleeding complications to the study drug will be the same as those for nonbleeding adverse events. If an investigator opinion of possibly, probably not, or not related to the study drug is given, an alternate etiology must be provided for the adverse event.

Adverse Event Collection Period

For randomized trials, there might be 2 different types of subjects who will be followed up for adverse events: (1) subjects considered angiographic or exclusion failures who do not proceed to randomization owing to the lack of eligible vascular occlusion and (2) all randomized subjects. These 2 types of subjects will be followed up for nonserious and serious adverse events for different time periods, as described next.

Subjects Considered Angiographic Exclusions

It is suggested that subjects considered angiographic or other image-based exclusions be monitored for all adverse events (serious and nonserious) from the signing of the study-
specific informed consent through a maximum of 24 hours after completion of the cerebral angiogram or other image based procedure or initiation of alternative stroke therapy, whichever comes first. Procedural complications should be summarized for angiographic exclusions with frequencies and percentages. The number and percentage of angiographic exclusions with bleeding complications other than ICHs should be computed. Adverse events starting before the start of the screening angiogram or ≥24 hours after the start of the screening angiogram might not necessarily be included in this summary. These recommendations are intended to ensure that proper safety guidelines occur for all potential ITT patients. The results are not required for publication.

All Randomized Subjects
All randomized subjects, whether they receive randomized therapy or not, should be monitored for serious and nonserious adverse events as presented: (1) From the time when the subject signs the study-specific informed consent form to the time of randomization, all adverse events (serious and nonserious) that are considered to be causally related to the study design and/or procedures might be collected. (2) From the time of randomization to the end of the postrandomization adverse event collection period (30 days after randomization), all adverse events (serious and nonserious) might be collected. (3) From 30 days after randomization to 90 days after randomization (the time of the 90-day follow-up assessments), only deaths might be collected.

Summary
Complications and adverse events are well defined and not expected to vary considerably for newly developed drugs under study. However, different treatment actions such as devices might necessitate inclusion of new adverse event types, eg, those related to perforations or distal emboles.

Recommendations for reporting are as follows: (1) Adverse events are reported separately for excluded and randomized subjects. (2) For randomized patients, adverse events are reported for 30 days and deaths for 90 days after randomization. For excluded subjects, adverse events are reported for 24 hours after the procedure that excluded the subject. (3) For case series, adverse events are reported for 30 days and deaths for 90 days after angiography or after treatment. (4) Adverse events are divided as hemorrhagic and nonhemorrhagic. (5) ICH is reported as symptomatic (increase in NIHSS ≥4) and asymptomatic. (6) Adverse events are reported as major/minor by the criteria stated previously. (7) The relation of the adverse event to the study drug must be reported.

Comparison Between Treatment Groups/Analysis
Randomization and Blinding
Techniques of comparison and analysis will depend on whether the study is a randomized trial or case series. The major advantage of a trial, over an observational study or case series, is the ability to demonstrate causality. In particular, randomly assigning the intervention can eliminate the influence of confounding variables, and blinding can eliminate the possibility that the observed effects of the intervention are due to other treatments or to biased ascertainment.119 Thus, appropriate randomization and blinding must be assured.

Randomization
A Central Randomization Center (CRC) independent of the study sponsor should be utilized to assign subjects to the different treatment and control groups. Once a subject has been deemed acceptable for the study, having met all entrance criteria that includes clinical, CT/MR scans, and angiographic criteria and having given informed consent, the CRC should be contacted for trial randomization. The CRC will need to know, for example, whether all entrance criteria have been met, including written informed consent, whether cerebral angiography has been performed documenting an occlusion in the requested vascular territory that is being studied, how much time has passed since symptom onset to randomization, and what is the subject’s total screening NIHSS score. After this information has been provided, the CRC will identify a treatment code, which will then be provided to the site. The study pharmacy at each center should have been supplied with a list of treatment codes and the corresponding treatment group. After receipt of the treatment code from the CRC, the study pharmacist should consult the treatment code list and prepare the corresponding treatment.

Blinding
Study drug administration might have to be open-label. However, neurologic and functional assessments performed at defined time points (eg, 7 to 10 days, 30 days, and 90 days) after the initiation of treatment should be performed by examiners blinded to the subject’s treatment and angiographic outcome. In addition, a Core Laboratory should assess the results of the CT and MR studies, as well as the angiograms, in a manner blinded to treatment assignment and clinical outcome.

Intention to Treat
Analyses should be performed for 3 subject populations: randomized subjects (ITT), subjects treated as randomized, and evaluable subjects. Randomized subjects should be defined as all subjects randomized to treatment or control. The population of subjects treated as randomized should include all subjects randomized to treatment who received at least some thrombolytic agent and all subjects randomized to control who did not receive a thrombolytic agent. The evaluable subject population should be defined as all subjects who did not have certain protocol deviations as specified by the project team. This is the same as the target population defined in the ECASS-I trial.8 Analysis of this subpopulation is necessary to distinguish treatment effect in the intended population from the effect of treating unintended patients included as protocol violations. A complete analysis for each of the 3 populations is required. Data might be summarized by using confidence intervals and the Statistical Analysis System (SAS Institute, Inc) probability values and should be based on 2-tailed tests.
Study Start Time
For subjects treated as randomized, in analyses for all parameters except adverse events, the determination for study entrance should be defined to be the time for the start of the thrombolytic infusion or activation of the thrombolytic device, respectively, and the start date/time of the control infusion for the control group. For subjects treated as randomized, in analyses of adverse events, the determination for the study entrance start time should be defined as the randomization contact date/time. For randomized but not-treated subjects, the determination of the study entrance for start time should be defined as the randomization contact date/time for all parameters except procedural complications. In analyses of procedural complications, the determination for study entrance for start of the study time for all subjects should be defined as the local start date/time of the screening angiogram to not exclude angiographic complications that might occur before randomization. In all angiographic exclusion analyses, the determination for start of the study time should be defined as the local start date/time of the screening angiogram. For all variables except the NIHSS score, the final value obtained before study start time should be used as the baseline value. For the analyses of changes from baseline and the analysis of baseline data for NIHSS score, the first value obtained before study start time should be used as the baseline value.

Analysis
Demographics should be summarized. Medical and cerebrovascular/cardiovascular histories should be summarized. Age, height, and weight should be summarized with means, standard errors, standard deviations, and ranges. Summary statistics should be computed for each treatment group. Summary statistics should be calculated within the subgroups of male and female subjects, as well as for combined genders. Means should be compared between treatment groups by a 1-way ANOVA. Frequencies and percentages should be computed for the following demographic parameters: gender, race, race/gender, and age. Frequencies and percentages should also be computed for the following baseline characteristics: general medical history items and cerebrovascular/cardiovascular medical history items. The percentages should be compared between treatment groups with Fisher’s exact tests. The duration of stroke symptoms should be summarized. However, duration of symptoms relative to hospitalization should be summarized only for subjects who are admitted to the hospital after the onset of symptoms (some subjects might be admitted to the hospital for other reasons before the onset of stroke), and duration of symptoms relative to IA thrombolysis start times should be summarized only for subjects who are randomized to and received thrombolysis. The duration of stroke symptoms (in hours) relative to hospitalization, first angiogram, randomization, and thrombolysis start times (thrombolysis subjects treated as randomized only) should be summarized for each treatment group with means, standard errors, standard deviations, medians, and ranges. Means should be compared between treatment groups by a 1-way ANOVA.

The diagnosis and suspected source and etiology of the occlusion should be summarized, with frequencies and percentages for each treatment group. The percentages should be compared between treatment groups with Fisher’s exact tests.

CT scan data should be summarized. Frequencies and percentages should be computed for each treatment group for the parameters of interpretation (abnormal, normal), technical adequacy (adequate, inadequate), hyperdense MCA sign (absent, present), involvement of greater than one third of the MCA territory (ECASS violators), and involvement of anatomic landmarks according to the ASPECTS scoring system. In addition, for both screening and follow-up CT scans, the frequencies and percentages of subjects in each group with the presence of edema and the presence of mass effect; the pathology types of hemorrhage (hemorrhagic infarcts and parenchymal hematoma, as defined earlier); or infarct should be calculated. With respect to either edema or mass effect, when a subject has multiple abnormalities and/or pathology types and edema/mass effect is present for at least 1 abnormality/pathology type, edema/mass effect should be defined to be present for the subject. When a subject has no lesions and the interpretation of the CT scan is normal, the subject should be counted as having absence of edema and mass effect. Also, when a subject has edema/mass effect present but the pathology type is not specified, the subject should be counted as having edema/mass effect present. The numbers and percentages of subjects with the presence of the pathology types of hemorrhage, hematoma, infarct (any, old, new), tumor, and other should also be calculated. When a subject has multiple abnormalities and a pathology type is associated with 1 or more of the abnormalities, the subject should be counted only once for that pathology type. The percentages should be compared between treatment groups with Fisher’s exact test for a 2×2 table.

If baseline CT is replaced by a baseline MR scan, the same analysis procedures should be performed. However, neither the hyperdense MCA sign nor the ECASS definition of more than one third of the MCA territory is sufficiently defined for MR yet for anterior-circulation strokes.

Angiographic data should be summarized. Frequencies and percentages should be computed for each treatment group for the proximal extent of the occlusion and whether the occlusion is partial or complete (TICI grade). Subjects should be categorized as complete responders, partial responders, and nonresponders for the angiographic outcomes of recanalization and restoration of distal flow at predetermined set time points, e.g., 60 and 120 minutes, after initiation of study drug infusion. Summaries of the TICI categories should be done for all study populations. For randomized trials, all analyses should be based on a Core Radiology laboratory assessment that is blinded to treatment and should be performed for the different TICI categories, unless otherwise specified. Treatment groups should be compared with respect to the distribution of proximal extent of the occlusion and complete versus partial occlusions with Fisher’s exact test.

The primary reasons given as to why subjects are angiographic exclusions should be summarized, with frequencies and percentages. Demographics should be summarized for angiographic exclusions. Baseline total NIHSS scores should
be summarized for angiographic exclusions with means, medians, standard errors, standard deviations, and ranges. General medical history, cerebrovascular/cardiovascular medical history, and diagnosis and etiology of the thrombus should be summarized with frequencies and percentages for angiographic exclusions. The results of the screening non-contrast CT scan and the screening MR for angiographic exclusions should be summarized. The duration of symptoms relative to hospitalization and the first angiogram should be summarized for angiographic exclusions with means, standard errors, standard deviations, medians, and ranges. Subjects who are admitted to the hospital before the onset of symptoms should be excluded from the analysis relative to randomization.

Administration of the thrombolytic agent should be summarized by bolus doses (if any), total volume infused, total amount of drug given, total infusion time, rate of infusion, and total elapsed time. Each variable should be summarized with means, medians, standard errors, standard deviations, and ranges. The numbers and percentages of thrombolytic subjects who did not receive study drug infusion should be calculated by reason. Multiple reasons for not receiving study drug might exist, but each subject should be counted no more than once for any reason. The numbers and percentages of thrombolyis subjects who prematurely terminated study drug infusion should be calculated by reason.

An analysis of hematology and chemistry data should be performed. Chemistry data should be included in analyses when the measurement was obtained in the time interval of >0 to 48 hours (relative to study start). When multiple values are included in a time interval, the measurement done at the time closest to the scheduled time should be used. When >1 time is of equal proximity to the nominal time, the data collected after the scheduled time should be used. In addition, each subject’s nadir value should be determined for each hematology parameter. For each treatment group, the baseline values, postinfusion values, and the change from baseline values should be summarized at each time point with means, medians, and ranges for each parameter. Only subjects having both a baseline value and a posttreatment value should be included in analyses at each time point for each parameter.

Neurologic deficit should be assessed as follows. The baseline total NIHSS score should be summarized for all study population groups. Total scores should be summarized with means, standard errors, standard deviations, medians, and ranges for each treatment group. Means should be compared between treatment groups by a 1-way ANOVA. Strata might be defined by using categories of NIHSS such as <10, 10 to 20, and >20. Analyses of total NIHSS scores should impute a value of 0 for death by using the same imputation conventions described for the modified Rankin analyses. As part of the primary methodology, carry-forward methods might be used. In addition, when a subject is missing a score for a time point after imputing for deaths and carrying-forward values, then the subject might be considered a failure for that time point and given a value of 0. As a secondary analysis, carry-forward methods should not be implemented, and subjects without values for particular time points should not be given a value of 42. The number and percentage of subjects with a total NIHSS score of 0 or 1 should be computed at each visit within each stratum for each treatment group. Changes from baseline in total NIHSS score at each time point should be summarized with means, standard errors, medians, and ranges for each treatment group. In all analyses of changes from baseline, individual NIHSS items with scores of 9 (indicating not applicable) at baseline or a time point should be deleted from the total score at baseline and the time point.

Functional outcome might be assessed with the BI and the mRS. BI scores might be summarized for all study population groups. Analyses of total BI scores should impute a value of 0 for death by using the same imputation conventions described for the modified Rankin analyses. As part of the primary methodology, carry-forward methods might be used. In addition, when a subject is missing a score for a time point after imputing for deaths and carrying-forward values, then the subject might be considered a failure for that time point and given a value of 0. As a secondary analysis, carry-forward methods should not be implemented, and subjects without values for particular time points should not be given a value of 0. For each stratum, the numbers and percentages of subjects with a total BI score ≥60 and ≥85 should be computed at each visit for each treatment group. Historical data from the BI and the mRS should be summarized for all study population groups. Total scores based on the BI and mRS should be summarized with means, standard errors, standard deviations, medians, and ranges for each treatment group. Means should be compared between treatment groups with a 1-way ANOVA. Strata might be defined by using categories of NIHSS such as <10, 10 to 20, and >20.

Quality of life might be assessed with EuroQol. This information is unlikely to be available before intervention, and therefore historical data cannot be evaluated. Total scores at 90 days should be summarized with means, standard errors, standard deviations, medians, and ranges for each treatment group. Means should be compared between treatment groups by a 1-way ANOVA. Strata might be defined by categories such as <10, 10 to 20, and >20 for screening total NIHSS score.

Efficacy analyses might be performed for all study population groups and should include an analysis of confidence intervals. Secondary analyses should be performed with evaluable data. The primary end point for the study most likely will be the percentage of subjects with a Rankin score ≤1 to 2 at 90 days, a predetermined NIHSS score, and a predetermined BI. The number and percentage of subjects with a Rankin score of ≤1, ≤2, and ≥5 should be computed at each visit. Note that for all analyses with 2 response categories, each mean score should be equivalent to the proportion of responders, eg, the proportion of subjects with a Rankin score of 2 or less or 1 or less, respectively. As secondary analyses, the following baseline parameters that are considered to be potential prognostic factors for stroke outcome should be used as stratification factors: investigative site, history of diabetes, prior use of platelet-inhibiting medication (aspirin, dipyridamole, ticlopidine, or nonsteroidal anti-inflammatory agents), age, proximal extent of occlu-
sion, right or left cerebral hemisphere, and time to treatment. The number and percentage of subjects with each Rankin score should also be computed for each treatment group within each stratum.

Adverse events might be analyzed as follows. Deaths occurring through the 90-day follow-up should be summarized. To account for possible late follow-up visits, deaths reported before 120 days (that occurred within 90 days of the procedure) should be counted. The number and percentage of deaths in each treatment group should be computed.

Adverse events other than death starting within 30 days from randomization might be summarized by treatment group with frequencies and percentages. All ICHs and the subset causing neurologic deterioration should be summarized by bleeding category, relation to study drug infusion, screening NIHSS score (<10, 10 to 20, >20), and baseline serum glucose (<200 mg/dL, >200 mg/dL). Bleeding complications starting before randomization should not be included in analyses. Additional summaries might be done for ICHs (all and those causing neurologic deterioration) starting within 24 to 36 hours after randomization.

Other adverse events, including procedural complications, might be summarized by treatment group with frequencies and percentages. A listing of all adverse events not included in analyses should be created. For analyses by severity, the most severe adverse event should be selected for each subject. Similarly, for analyses by relation, the adverse event most related to study drug should be selected for each subject. All safety analyses should be performed for all study populations. One interim analysis that includes a futility assessment is suggested to be performed at a defined time point.

Summary

Patients undergoing a clinical study for IA thrombolysis should undergo randomization by a CRC, independent of the study sponsor. A double-blind, prospective, randomized trial is recommended, however, if this is not feasible; in that case, blinding of the stroke neurologist at the critical clinical time points of 30 days and 90 days is recommended.

A variety of data are collected from each patient during a trial, and analysis must be stratified. Different groups of patients might be defined (eg, all, treated as randomized, etc). In each of these groups, baseline demographic data, inclusion and exclusion criteria, physiologic parameters, outcomes, and complications are collected, and the correct analysis or their occurrence and interaction requires a detailed statistical approach.

Recommendations for reporting for randomized trials include the following: (1) technique of randomization; (2) technique of blinding; (3) separate analyses for the 3 subject populations: ITT, treated as randomized, and evaluable subjects; (4) separate analysis of angiographic exclusions. For randomized trials or case series, recommendations are (1) analyses of demographics, duration of stroke symptoms, source and etiology of occlusion, administration of lytic agent, and changes in laboratory data; (2) analyses of CT/MR results, including abnormal versus normal, technical adequacy, hyperdense MCA sign, size of anterior circulation infarct, and presence of edema/mass effect/hemorrhage; (3) analyses of angiographic results, including occlusion location and severity and response to lysis; and (5) analyses of neurologic deficit, functional outcome, quality of life, and adverse events stratified for severity of initial neurologic deficit.

Costs

In general, it has been recognized that the disadvantages of IA therapy lie in the cost and delay. For IA therapy to be available for emergency care of ischemic stroke, personnel and equipment must be in constant readiness.

Some approximate numbers on the costs of 1 day at a major teaching hospital for a patient with an acute ischemic stroke would be (1) $6000 to $8000/d for an intensive care unit; (2) $3000 to $5000/d for a stroke step-down unit; and (3) $2000 to $4000/d for a regular bed.

After IA thrombolysis, a patient would stay, depending on their clinical status, for 1 or 2 days in the ICU and for another 5 to 7 days in the step-down unit. Most likely, the patient would be transferred to rehabilitation directly from the step-down unit. The cost of thrombolytic and adjunctive drugs or thrombolytic devices might also be a significant contribution to hospital costs. Therefore, these costs from the thrombolytic treatment should be reported.

Summary

A rough estimate of costs should be reported by using cost of thrombolytic and adjunctive drugs and devices from the lytic treatment, number of ICU days, and number of hospital days in an acute care facility. Number of days in a rehabilitation facility might also be helpful to report. A complete cost analysis is beyond the scope of these guidelines.

Conclusions

Divergent entry criteria and outcome measures have been used in the past for acute stroke studies. The compromise between restrictive inclusion criteria, which might increase the likelihood to demonstrate a treatment-related benefit, and a sufficient number of eligible patients has to be defined for each trial. However, even with apparently detailed definition of the patient population, eg, restricting patient enrollment to M1 and M2 occlusions only, patients still might demonstrate considerable variability, depending, for example, on the amount of collaterals. Similarly, different outcome measures might be appropriate depending on the drug or device under study. For the assessment of patient outcome, not only do several different assessment scales exist in parallel, such as the Rankin score, BI, or mortality alone, but also different thresholds within the assessment scales might have been used (eg, mRSS of ≤1 versus ≤2). Inclusion criteria and outcome assessment must be defined by each sponsor or principal investigator of a trial, depending on the expected effect of the new drug or device under study, while carefully reviewing the results of previous, similar trials.

Evaluation of physiologic parameters before and after the intervention is important. Most critical is blood pressure monitoring and treatment; high normal blood pressure values are necessary to optimize cardiac output and maintain sufficient cerebral perfusion pressure, in particular, to preserve the
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penumbra, the tissue at risk. On the other hand, hypertension has to be prevented, because it might increase the risk of ICH.

This document offers a rationale for the different considerations that might be important during the design of a clinical trial for IA thrombolysis in acute stroke. Moreover, previously used and established definitions for patient selection, outcome assessment, data analysis, etc., are provided, with some possible variations on specific cutoffs. Thus, this document is targeted to help an investigator to critically review the scales and scores used previously. In addition, this document provides recommendations for uniform reporting that are applicable to both randomized trials and case series. A summary of recommendations for reporting is included in Table 6.

In addition to established criteria, technology is continuously evolving, and imaging techniques have been introduced that offer new insights into the pathophysiology of acute ischemic stroke. A better patient stratification might be possible if CT or MR brain scans are not only used as exclusion criteria but are exploited further to provide individual inclusion and exclusion criteria based on tissue physiology. Furthermore, imaging techniques might be used as a surrogate outcome measure in future trials. The context of a controlled study is the best environment to validate emerging imaging and treatment techniques. For the field to advance, not only do better drugs, devices, and techniques have to be developed but also advantage should be taken of technological progress in neuroradiologic imaging.

**References**


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Trial Design and Reporting Standards for Intra-Arterial Cerebral Thrombolysis for Acute Ischemic Stroke
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for the Technology Assessment Committees of the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology

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In the article “Trial Design and Reporting Standards for Intra-Arterial Cerebral Thrombolysis for Acute Ischemic Stroke” by Higashida and Furlan,¹ the following writing committee members were omitted from the list of authors: Heidi Roberts, MD; Thomas Tomsick, MD; Buddy Connors, MD; John Barr, MD; William Dillon, MD; Steven Warach, MD; Joseph Broderick, MD; Barbara Tilley, PhD; and David Sacks, MD. The submitting author regrets the omission.

Below is the corrected citation and author list: